Volume 27, Number 4, 1989

CIRCULATORY SHOCK

THE SHOCK SOCIETY PRESENTS
THE TWELFTH ANNUAL CONFERENCE ON SHOCK
MARCO ISLAND, FLORIDA
JUNE 9–12, 1989

Alan R. Liss, Inc.

ISSN 0002-6213

CIRCULATORY SHOCK

OFFICIAL JOURNAL OF
THE SHOCK SOCIETY AND OF
THE EUROPEAN SHOCK SOCIETY

Circulatory Shock (ISSN 0092-6213) is published by Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003.
Subscription price: Volumes 27, 28, and 29, 1989, twelve issues: $549 in US; $597 outside US. Members of the Shock Society can obtain the Journal at a reduced subscription rate. For details, please contact the Society. All subscriptions outside North America will be sent by air. Payment must be made in US dollars drawn on a US bank. **Change of Address:** Please send to publisher six weeks prior to move; enclose present mailing label with change of address. **Claims for Missing Issues:** Claims cannot be honored beyond four months after mailing date. Duplicate copies cannot be sent to replace issues not delivered because of failure to notify publisher of change of address. **Cancellations:** Subscription cancellations will not be accepted after the first issue has been mailed. Exclusive agent in Japan: Igaku Shoin Limited, Foreign Department, 1-28-36 Hongo, Bunkyo-ku, Tokyo 113, Japan. ¥ 144,400 for 1989 (Air Cargo Service only). **Indexed by:** Current Contents/Life Sciences-Science Citation Index • Chemical Abstracts • Index Medicus • BIOSIS-Data Base • Excerpta Medica • ISI-Soviet Union. Printed in the United States of America.

The paper on which this journal is printed adheres to the requirements for library/archival stability.

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

DTIC FILE COPY

1

1a. REPORT SECURITY CLASSIFICATION

1b. RESTRICTIVE MARKINGS

2a. SECURITY CLASSIFICATION AUTHORITY

3. DISTRIBUTION/AVAILABILITY OF REPORT

Distribution to general public.

AD-A218 036

5. MONITORING ORGANIZATION REPORT NUMBER(S)

6a. NAME OF PERFORMING ORGANIZATION
Reticuloendothelial Society

6b. OFFICE SYMBOL (If applicable)

7a. NAME OF MONITORING ORGANIZATION

6c. ADDRESS (City, State, and ZIP Code)
c/o Dr. Sherwood M. Reichard
Medical College of Georgia
Augusta, GA 30912

7b. ADDRESS (City, State, and ZIP Code)

8a. NAME OF FUNDING/SPONSORING ORGANIZATION
Office of Naval Research

8b. OFFICE SYMBOL (If applicable)

9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
N00014-89-J-1886

8c. ADDRESS (City, State, and ZIP Code)
800 North Quicy Street
Arlington, Virginia 22217-5000
Code: 1141SB

10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
Symposia at the 12th Annual Conference on Shock

12. PERSONAL AUTHOR(S)
Irshad H. Chaudry

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 1June 89 TO 1 Feb 90	1 Feb 90	

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

DTIC
ELECTE
FEB 14 1990
S B D

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Dr. Sherwood M. Reichard	404 721-2601	

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE

TWELFTH ANNUAL CONFERENCE ON SHOCK
Marco Island, Florida
Friday, June 9–Monday, June 12, 1989

PROGRAM COMMITTEE
CHAIR
Irshad H. Chaudry, PhD, Michigan State University

MEMBERS
H. Richard Adams, DVM, PhD, University of Missouri
John W. Holaday, PhD, Walter Reed Army Institute of Research

AWARDS AND HONORS COMMITTEE CHAIR
David G. Reynolds, PhD, University of South Florida

MEMBERS
James A. Cook, PhD, Medical University of South Carolina
Tracy K. McIntosh, PhD, University of Connecticut Health Center
Steven A. Gould, MD, Michael Reese Hospital
J. Raymond Fletcher, MD, PhD, St. Thomas Hospital

Program

PROGRAM

Friday, June 9

1:00 to 6:00 p.m.	Registration	North Wall
1:00 to 6:00 p.m.	Council Meeting	Mainsail
7:30 to 8:30 p.m.	Keynote Address: "Evolution of Modern Concepts of Hypovolemic Shock" **Frank R. Lewis, M.D.** President-Elect San Francisco General Hospital	Salon CD
8:30 to 9:30 p.m.	Reception	Quarterdeck

Saturday, June 10

7:00 to 8:00 a.m.	Editorial Board Breakfast	Orlando
7:30 a.m. to 6:00 p.m.	Registration	North Wall
7:30 to 9:30 a.m.	Poster Session I (With Continental Breakfast) A. "Cardiovascular Responses Following Shock," papers 1–14. B. "Cytokines, Eicosanoids and Hormones," papers 15–45. C. "Pharmacologic Agents," papers 46–58.	Exhibit Hall
9:30 a.m. to 12:00 p.m.	Symposium I: "Cytokines and Lymphokines Following Hemorrhage and Sepsis" Presiding: **J. Wesley Alexander, M.D.** University of Cincinnati and **Irshad H. Chaudry, Ph.D.** Michigan State University	Salon CD

1) "Relationship Between Eicosanoids, Cytokines and Lymphokines"
J. Wesley Alexander, M.D.
University of Cincinnati
2) "TNF, Oxygen Radicals and Tissue Injury"
Peter Ward, M.D.
University of Michigan
3) "Protective Effects of TNFα in Vascular Injury"
Asrar B. Malik, Ph.D.
Albany Medical College
4) "*Gamma-Interferon*"
Scott Durum, Ph.D.
NCI-FCRF
5) "Sepsis Induced Alterations in Cytokines"
Eugene Faist, M.D.
University of Munich, West Germany
6) "Colony Stimulating Factor and IL-1 Release in Sepsis"
Frank B. Cerra, M.D.
University of Minnesota
7) "Hemorrhage Induced Alterations in Lymphokines"
Irshad H. Chaudry, Ph.D.
Michigan State University

10:15 to 10:45 a.m. Coffee Available
12:00 to 1:30 p.m. Buffet Lunch — Salon FG
1:45 to 3:15 p.m. Young Investigator Awards Session, papers 59–62 — Salon CD
Presiding: **David G. Reynolds, Ph.D.**
University of South Florida

1) "Macrophages Induce Neutrophil Emigration by a Non-CD18 Mechanism of Adherence"
William J. Mileski
University of Washington, Seattle
2) "Effect of Endothelial Cell Confluence on Cellular Glutathione Levels and Resistance to Oxidative Injury"
Robert Holman
University of Washington, Seattle
3) "Influence of a Linseed Oil Enriched Ration on the Response to Endotoxin in Horses"
Michelle M. Henry

University of Georgia, Athens
4) "Oxygen Radicals Disturb Endothelial Cell Morphology and Intracellular Free Calcium Dynamics"
Dido Franceschi
Case Western Reserve University, Cleveland

3:15 to 3:30 p.m. Coffee Available

3:30 to 6:00 p.m. Symposium II: "Hazards of Blood Transfusion and Alternatives for Resuscitation" — Salon GHJ
Presiding: **J. Carlton Hsia, Ph.D.**
Hemosol, Inc., Canada and
Gerald S. Moss, M.D.
Michael Reese Hospital and University of Chicago
1) "Relative Safety of Whole Blood Transfusion and Its Components"
Richard Condie, Ph.D.
Minnesota ALG Program
2) "Chemistry and Animal Testing of Cross-Linked Hemoglobin"
Timothy N. Estep, Ph.D.
Baxter Health Care Corp., Round Lake, IL
3) "Hemosafe—A Heat Pasteurized Oxygen Carrying Resuscitative Fluid"
J. Carlton Hsia, Ph.D.
Hemosol, Inc., Canada
4) "Effect of Hemoglobin-Based Substitutes on the RES"
A. Gerson Greenburg, M.D., Ph.D.
Brown University/The Miriam Hospital, Providence, RI
5) "Vasoconstrictive Activity of Hemoglobin-Based Blood Substitutes"
C. Robert Valeri, M.D.
Naval Blood Research Laboratory, Boston, MA
6) "Safety, Efficacy and Immunogenicity of Hemoglobin-Based Blood Substitute"
Thomas M.S. Chang, M.D., Ph.D.
Artificial Cell and Organ Research Center

	McGill University, Canada 7) "Biochemistry and Animal Testing of Polymerized Pyridoxylated Hemoglobin" **Lakshman R. Sehgal, Ph.D.** Michael Reese Hospital, Chicago, IL 8) "Clinical Trials of Polymerized Pyridoxylated Hemoglobin" **Gerald S. Moss, M.D.** Michael Reese Hospital and University of Chicago	
6:30 to 7:30 p.m.	Reception	Salon EF
7:30 to 8:30 p.m.	Dinner	Salon CD
8:30 to 9:30 p.m.	*Speaker:* **Lee Van Lenten, M.D.** Chief Physiological Sciences Section Biophysics and Physiological Sciences Program, NIGMS, NIH "NIH—Trauma Research/Training Programs"	Salon CD

Sunday, June 11

6:30 to 7:30 a.m.	Presidential Run	
7:30 a.m. to 6:00 p.m.	Registration	North Wall
7:30 to 9:30 a.m.	Poster Session II (With Continental Breakfast) D. "Animal Models," papers 63–76. E. "Metabolism Following Shock/Trauma," papers 77–93. F. "Oxygen Metabolites," papers 94–110.	Exhibit Hall
9:30 a.m. to 12:00 p.m.	Symposium III: "Calcium and Magnesium Related Cellular Alterations in Shock-Like States" Presiding: **Mohammed M. Sayeed, Ph.D.** Loyola University and **Donald Trunkey, M.D.** Oregon Health Sciences Center 1) "The Role of Calcium in Myocardium During Sepsis" **Donald Trunkey, M.D.** Oregon Health Sciences Center 2) "Calcium Sensitive and Calcium Insensitive Proteolysis in Skeletal Muscle" **Alfred Goldberg, Ph.D.** Harvard Medical School	Salon CD

	3) "Role of Calcium in Myocardial Dysfunction During Shock" **Janet L. Parker, Ph.D.** University of Missouri	
	4) "Altered Intracellular Calcium Regulation During Shock" **Mohammed M. Sayeed, Ph.D.** Loyola University Stritch School of Medicine	
	5) "Role of Magnesium in Vascular Smooth Muscle Function During Shock" **Burton M. Altura, Ph.D.** SUNY Downstate Medical Center	
10:15 to 10:45 a.m.	Coffee Available	
12:00 to 1:00 p.m.	Business Meeting	Qdeck 7–10
	Free Afternoon	

Monday, June 12

7:30 a.m. to 6:00 p.m.	Registration	North Wall
7:30 to 9:30 a.m.	Poster Session III (With Continental Breakfast) G. "Organ Function Following Shock/Trauma," papers 111–128. H. "Resuscitation Following Shock/Trauma," papers 129–147. I. "Clinical Applications," papers 148–165.	Exhibit Hall
9:30 a.m. to 12:00 p.m.	Minisymposium I: "Recent Advances in the Treatment of Experimental Shock/Ischemia and Their Clinical Implications," papers 166–174. Presiding: **Arthur E. Baue, M.D.** St. Louis University Medical Center and **Allan M. Lefer, Ph.D.** Jefferson Medical College	Salon B
9:30 to 9:35 a.m.	Introduction: **Allan M. Lefer, Ph.D.**	
9:35 to 9:50 a.m.	1) "Protective Effects of a Novel Non-Glucocorticoid 21-Aminosteroid (U-74006F) During Traumatic Shock in Rats" **Nubuo Aoki** Thomas Jefferson University, Philadelphia	
9:50 to 10:05 a.m.	2) "Efficacy and Toxicity of Lazaroid	

(U74006F) in Neonatal Endotoxemia"
Susan D. Semrad
University of Wisconsin, Madison

10:05 to 10:20 a.m. 3) "Platelet Activating Factor (PAF) Antagonist Improves Survival and Attenuates Eicosanoid Release in Lethal Endotoxemia"
J. Raymond Fletcher
Vanderbilt University, Medical Center, Nashville

10:20 to 10:35 a.m. 4) "Protective Effects of Acidified Sodium Nitrite ($NaNo_2$) Combined With Human Superoxide Dismutase (hSOD) in Myocardial Ischemia With Reperfusion"
Gerald Johnson III
Thomas Jefferson University, Philadelphia

10:35 to 10:50 a.m. 5) "Early Post Burn Lipid Peroxidation (Effect of Ibuprofen and Allopurinol)"
Cheryl LaLonde
Longwood Area Trauma Center, Boston

10:50 to 11:05 a.m. 6) "Cross-Linked Hemoglobin Solution as a Resuscitative Fluid Following Hemorrhage in the Rat"
Diana S. Malcolm
Uniformed Services University of the Health Sciences, Bethesda

11:05 to 11:20 a.m. 7) "rCBF Following Fluid Resuscitation From Hemorrhagic Shock With Isotonic or 7.2% NACL With and Without a Subdural Mass"
John M. Whitley
Wake Forest University, Winston-Salem

11:20 to 11:35 a.m. 8) "Effect of Impaired Hepatic Mitochondrial Function (HMF) on Systemic Metabolism in Multiple Organ Failure (MOF) Patients and Its Treatment With ATP-$MgCl_2$"
Hiroyuki Hirasawa
Chiba University School of Medicine, Japan

11:35 to 11:50 a.m. 9) "Improved Survival From Hemorrhagic Shock With Inositol and

	ATP-$MgCl_2$ Administration" **Marc J. Shapiro** St. Louis University Medical Center, St. Louis	
11:50 to 12:00 p.m.	Closing Remarks: **Arthur E. Baue, M.D.**	
9:30 a.m. to 12:00 p.m.	Workshop I: "Endogenous Mechanisms in Coagulation and Anticoagulation Disorders During Shock" Presiding: **Houria I. Hassouna, M.D., Ph.D.** Michigan State University and **Fletcher B. Taylor, M.D.** Oklahoma Medical Research Foundation 1) "Baboon Septic Shock Model: Staging and the Role of the Vascular Endothelium and Hemostatic Factors" **Fletcher B. Taylor, M.D.** Oklahoma Medical Research Foundation 2) "Regulation of the Production and Effects of Tumor Necrosis Factor" **Steven Kunkel, Ph.D.** University of Michigan Medical Center 3) "Initiation of the Coagulation Mechanism in Shock" **Houria I. Hassouna, M.D., Ph.D.** Michigan State University 4) "The Role of Heparin in the Control of Disseminated Intravascular Coagulation (DIC)" **John A. Penner, M.D.** Michigan State University and the American Red Cross 5) "Effect of Acellular Oxygen Transport on the Hemostatic System" **Lowell E. McCoy, Ph.D.** Wayne State University	Salon C
10:15 to 10:45 a.m. 12:00 to 1:30 p.m.	Coffee Available Panel Discussion: (Buffet Luncheon) "Who Qualifies for Extended Critical Care and Who Gets It" Presiding: **William Sibbald, M.D.** University of Western Ontario and **Charles Sprung, M.D.** University of Miami	Qdeck

	Panel Members: Honorable **Christopher J. Armstrong** Associate Justice, Court of Appeals, Boston, MA **Abbyann Lynch, Ph.D.** Westminster Institute for Ethics and Human Values London, Ontario **Mary Ann Baily, Ph.D.** George Washington University	
1:45 to 3:45 p.m.	Minisymposium II: "Immunomodulation and Monoclonal Antibodies in the Treatment of Shock and Sepsis," papers 175–181. Presiding: **Mark A. Malangoni, M.D.** University of Louisville and **Charles L. Rice, M.D.** University of Washington, Seattle, WA	Salon B
1:45 to 1:50 p.m.	Introduction: **Mark A. Malangoni, M.D.**	
1:50 to 2:05 p.m.	1) "Efficacy of Post-Treatment With Anti-TNF Monoclonal Antibody in Preventing the Pathophysiology and Lethality of Sepsis in the Baboon" **Lerner B. Hinshaw** Oklahoma Medical Research Foundation and Chiron Corporation, Oklahoma City	
2:05 to 2:20 p.m.	2) "Temporal Responses of Cytokines In Vivo Following Inflammation and Trauma in Humans" **Joseph G. Cannon** New England Medical Center, Boston	
2:20 to 2:35 p.m.	3) "Relationship of TNFα to Biochemical, Hematological and Survival Response to Endotoxemia in Conscious Rats" **Giora Feuerstein** Uniformed Services University of the Health Sciences, Bethesda	
2:35 to 2:50 p.m.	4) "Cytokine Mediated Increases in Vascular Permeability (VP) In Vivo" **Joseph M. Hayes** University of Pittsburgh	
2:50 to 3:05 p.m.	5) "The Role of Protein Synthesis in Streptococcus Pneumoniae (S pneu) Induced Neutrophil (PMN) Emigration Into Lungs"	

	Robert K. Winn University of Washington, Seattle	
3:05 to 3:20 p.m.	6) "The Cardiovascular and Pulmonary Effects of Human Recombinant Tumor Necrosis Factor in the Conscious Rat" **Claudia Turner** Smith Kline & French Laboratories, King of Prussia	
3:20 to 3:35 p.m.	7) "An Alteration in Early T-Lymphocyte Activation Following Trauma" **David B. Hoyt** University of California, San Diego	
3:35 to 3:45 p.m.	Closing Remarks: **Charles L. Rice, M.D.**	
1:45 to 3:45 p.m.	Workshop II: "The Influence of Anesthesia and Restraint in the Response to Shock: Correlation With Humans" Presiding: **Steve Gould, M.D.** University of Chicago and **Richard B. Weiskopf, M.D.** University of California, San Francisco 1) "Anesthesia and the Hypovolemic *State*" **Richard B. Weiskopf, M.D.** University of California, San Francisco 2) "O_2 Transport in the Awake and the Anesthetized Primate" **Arthur L. Rosen, Ph.D.** Michael Reese Hospital and University of Chicago 3) "Chemical Restraint in Shock Research: Whose Decision" **H. Richard Adams, D.V.M., Ph.D.** University of Missouri-Columbia 4) "Anesthesia in the Injured Patient—The Real World" **Clifford M. Herman, M.D.** Harborview Medical Center, Seattle, WA	Salon C
3:45 to 4:00 p.m.	Coffee Available	
4:00 to 6:00 p.m.	Minisymposium III: "Organ Preservation: Potential Applications in Shock States," papers 182–188. Presiding: **Ronald Ferguson, M.D., Ph.D.**	Qdeck 1

Ohio State University Hospital and
Marie Foegh, M.D.
Georgetown University Medical Center

4:00 to 4:05 p.m. Introduction: **Marie Foegh, M.D.**

4:05 to 4:20 p.m. 1) "Endothelin: An Endothelial-Derived Peptide With Positive Inotropic Action in Arterial Smooth Muscle and Myocardium"
J.A. Allert
University of Missouri, Columbia

4:20 to 4:35 p.m. 2) "Evidence for Endotoxin Related Tumor Necrosis Factor (TNF) Release in Intestinal Ischemia-Reperfusion Injury
Michael G. Caty
Univeristy of Michigan Medical School, Ann Arbor

4:35 to 4:50 p.m. 3) "The Role of Toxic Oxygen Metabolites in the Pathogenesis of a New Model of Acute Hemorrhagic and Necrotic Pancreatitis"
Tsen-Long Yang
Johns Hopkins Medical Institutions, Baltimore

4:50 to 5:05 p.m. 4) "Oxygen-Radical-Mediated Acute Lung Injury: Enhancement of Xanthine Oxidase Activity By Histamine"
Hans P. Friedl
University of Michigan Medical School, Ann Arbor

5:05 to 5:20 p.m. 5) "Oxygen Free Radicals (OFRs): The Renal Hemodynamic Response"
John A.Galat
Case Western Reserve University, Cleveland

5:20 to 5:35 p.m. 6) "Hepatic Perfusion Abnormalities Produced by Synergism Between Platelet Activating Factor (PAF) and Complement"
William J. Schirmer
Case Western Reserve University, Cleveland

5:35 to 5:50 p.m. 7) "Role of Iron in Ischemia and Reperfusion"
Elaine P. Robinson
University of Minnnesota, St. Paul

5:50 to 6:00 p.m.	Closing Remarks: **Ronald Ferguson, M.D., Ph.D.**	
4:00 to 6:00 p.m.	Workshop III: "Gastrointestinal Bacterial Translocation During Stress Conditions" Presiding: **Edwin Deitch, M.D.** Louisiana State University and **Carol Wells, Ph.D.** University of Minnesota 1) "Route and Mechanisms of Bacterial Translocation" **Carol Wells, Ph.D.** University of Minnesota 2) "Burn, Trauma, Nutrition and Bacterial Translocation" **J. Wesley Alexander, M.D.** University of Cincinnati Medical Center 3) "Bacterial Translocation in Experimental Stress States" **Edwin A. Deitch, M.D.** Louisiana State University Medical Center 4) "Gut Permeability Alterations During Infection and Endotoxemia" **Thomas R. Ziegler, M.D.** Harvard Medical School	Qdeck 6
6:30 to 7:30 p.m.	Reception	Salon AB
7:30 to 8:30 p.m.	Dinner	Salon CD
8:30 to 9:30 p.m.	Speaker: **Walter Randall, Ph.D.** Loyola University, Stritch School of Medicine "The Use of Animals in Biomedical Research"	Salon CD

Abstracts

1 PNEUMONECTOMY ASSOCIATED WITH HEMORRHAGIC SHOCK CAUSES RIGHT HEART FAILURE DUE TO INCREASED PULMONARY VASCULAR RESISTANCE. H.Cryer, J.Yu, A.Roberts, J.Cue, C.Mavroudis. Univ. Louisville, Louisville, KY. 40292

Mortality approaches 100% in patients with hemorrhagic shock requiring pneumonectomy to control bleeding. We studied this problem in anesthetized open chest pigs. Group I (n=5) was bled to 50% of baseline MAP for 1 hour and resuscitated with Ringers lactate (RL) and shed blood (2 volumes RL/volume shed blood) to maintain baseline left ventricular (LV) end diastolic pressure for 3 hours. Group II (n=5) had left pulmonary hilar ligation without shock. Group III (n=9) had hemorrhagic shock+hilar ligation before resuscitation. We measured MAP; CO; HR; right ventricular (RV), LV, and pulmonary artery (PAP) pressures. We calculated stroke volume (SV, systemic vascular (SVR) and pulmonary vascular resistance (PVR).

All group I & II pigs survived. Four (44%) Group III pigs died from RV failure. Data from the 5 survivors in Group III compared to control Groups I and II 3 hours after initiating resuscitation, expressed as percent increases or decreases from baseline values were: ($p<.05$, ANOVA+Bonferroni, *Group III vs I, †Group III vs II).

GROUP	MAP	SV	PAP	PVR	SVR
Group I	-5±6%	-33±4%	+35±7%	+52±7%	+12±8%
Group II	+17±5%	-41±6%	+94±29%	+86±16%	+15±10%
Group III	-29±14%*†	-73±4%*†	+96±8%*	+252±52%*†	+10±6%

We conclude that PVR increased in Groups I and II and LV stroke volume decreased. However, in Group III, shock+pneumonectomy synergistically increased PVR enough to cause RV failure and insufficient LV stroke volume for effective resuscitation.

2 HYPERDYNAMIC CIRCULATION WITH ANTIBIOTIC KILLED GRAM$^+$ OR GRAM$^-$ BACTERIA. D. Dehring, G. Beerthuizen*, R. McGuire*, D. Traber, L. Traber. Univ Tx Med Branch, Shriners Burns Inst, Galveston, Tx 77550. (Supported by HL36286 and SBI #15872)

Endotoxin or live *Ps.aeruginosa* (*PS*) induce a delayed increase in cardiac index (CI) and decrease in mean arterial pressure (MAP) and total peripheral resistance index (TPRI), which mimic the hemodynamic changes of clinical sepsis. To determine if Gram$^+$ organisms cause the same change, *S. aureus* (*SA*) and *PS* bacteria were killed by exposure to gentamicin and nafcillin respectively. Chronically instrumented sheep were infused with *PS*(5×10^7 *PS*/min for 30-45 min until mean pulmonary artery pressure (PAP) was 40 mmHg; n=6) or *SA*(5×10^7 *SA*/min for 60 min; n=7). *SA* did not change the PAP while *PS* doubled it at 1 hr with mild persistant increases. *SA* increased the CI by 1-1.5 L/min/m^2 from 3-8 hrs with decreased TPRI from 3-6 hrs. *PS* induced an initial cardiovascular depression with decreased *CI* and increased *TPRI* from 3-4 hrs, but the CI then increased and vasodilation occurred from 8-18 hrs. The temperature increased by 1°C from 1-2 hrs in both groups with further increase of 1 C in *PS* from 3-5 hrs. The earlier hyperdynamic circulation in *KS* may be due to lack of myocardial depression with *KS*, but it is not due to differences in febrile response. The hyperdynamic circulation is not unique to Gram$^-$ bacteria.

		0	4	8	12 hrs
CI	*SA*	6.2 ± 0.4	7.6 ± 0.6^x	7.3 ±0.6^x	7.1 ± 0.6
L/min/m^2	*PS*	6.5 ± 0.1	5.2 ± 0.3^{x*}	7.8 ±0.4^x	7.6 ± 0.5^x
TPRI	*SA*	1171 ± 92	1000 ± 105^x	1019 ±108	1079 ± 99
Dynes·sec·cm^{-5}	*PS*	1174 ± 42	1646 ± 85^{x*}	856 ±49^x	920 ± 92

x = $p \leq 0.05$ within group * = $p \leq 0.05$ between groups

3 EFFECTS OF H_1 AND H_2 BLOCKERS ON MOBILIZATION OF MYOCARDIAL CARNOSINE TO HISTAMINE DURING COMPOUND 48/80-INDUCED SHOCK IN YOUNG RATS. J. Fitzpatrick*, H. Fisher* and L. Flancbaum UMDNJ-RWJMS and Rutgers Univ., New Brunswick, NJ 08903.

Histamine (HM) exerts profound effects on the cardiovascular system mediated by H_1 and H_2 receptors. We have shown that carnosine (CAR) is a non-mast cell reservoir for histidine (HIS), utilized for HM synthesis in shock. Compound 48/80, a mast cell degranulator, produces lethal stress and mobilization of myocardial CAR to HIS and HM in aged rats, which is prevented by a mast cell degranulation inhibitor, lodoxamide (L). This study was designed to evaluate the effects of H_1 and H_2 blockers on CAR mobi-

lization to HM during 48/80 induced shock in young rats. Methods: 50 male SD rats (125g) were put into 9 groups: 1-saline; 2-L; 3-H_1 blocker diphenhydramine (D); 4-H_2 blocker cimetidine (C); 5-48/80; 6-L+48/80; 7-D+48/80; 8-C+48/80; and 9-D+C+48/80. All rats survived and were sacrificed 30 min. after final injections and hearts analysed via HPLC. Results: Reduction in myocardial CAR ($p \leq .01$) and HIS ($p \leq .001$) and a simultaneous increase in HM ($p \leq .01$, $p \leq .001$) was seen in animals receiving 48/80 or C+48/80, respectively, compared to controls or groups pretreated with L, D, or D+C.

CPD	Saline	L	D	C	48/80	L+48/80	D+48/80	C+48/80	D+C+48
HIS	71.2±2.9	74.8±9.9	74.2±3.7	74.0±5.1	**58.1±5.4[b]**	72.9±3.0	74.3±9.4	**56.5±1.7[b]**	73.9±4.7
HM	7.2±1.6	7.8±0.4	7.8±1.2	6.6±2.0	**10.4±1.6[a]**	7.3±1.9	6.4±1.5	**11.7±1.8[b]**	8.2±1.4
CAR	18.6±1.3	19.6±2.6	19.4±3.2	19.2±3.3	**13.7±2.6[a]**	18.1±2.4	18.4±4.9	**14.0±2.0[a]**	21.9±1.2

* mean µg/g ± SD. a = $p \leq 0.01$, b = $p \leq 0.001$ (ANOVA with multiple range test)

Conclusions: 48/80-induced shock increases mobilization of CAR and HIS to HM, which supports CAR as a non-mast cell HM source during stress. L or D prevented mobilization by blocking HM release or its effects on H_1 receptors, respectively. Increased mobilization of CAR and HIS to HM during H_2 blockade by C suggests a separate role for H_2 receptors in 48/80-induced shock which requires further study.

4 CIMETIDINE INCREASES MORTALITY DURING COMPOUND 48/80-INDUCED SHOCK IN RATS. L. Flancbaum, J. Fitzpatrick*, and H. Fisher* UMDNJ-RWJMS, New Brunswick, NJ 08903.

The roles of histamine and H_1 and H_2 receptors in shock are uncertain. We found that treatment of aged rats with compound 48/80 (mast cell degranulator) produced lethal (LD_{99}) stress (hypotension and bronchospasm mediated by H_1 receptors) which was completely prevented by lodoxamide (L, a mast cell degranulation inhibitor). This study evaluated the role of H_1 and H_2 receptors during 48/80-induced shock in young 125g, mature 250g and aged 500g rats. Methods: To assess survival, 65 male 125g, 65 250g and 30 500g SD rats were put in groups and treated IP with: saline; 48/80; L+48/80; H_1 blocker diphenhydramine (D)+48/80; H_2 blocker cimetidine (C)+48/80; or D+C+48/80. Rats were observed for 30 min. or until death. Results: All 125g rats survived. Of the 250g rats, 50% of 48/80-treated and 100% of C+48/80 treated rats died; all others survived. All 500g 48/80 and C+48/80 treated rats died; all others survived. For all ages, survival differences between saline, 48/80, and C+48/80 treated rats were highly significant ($p \leq 0.0001$). Survival times (40 min - 250g; 30 min - 500g) are recorded below:

Time	Saline	48/80	L+48/80	D+48/80	C+48/80	D+C+48/80
250g Min±SD	40 ± 0	**28.3 ± 3.1**	40 ± 0	40 ± 0	**21.9 ± 3.8**	40 ± 0
500g Min±SD	30 ± 0	**19.4 ± 2.3**	30 ± 0	30 ± 0	**13.2 ± 2.6**	30 ± 0

Both 48/80 and C+48/80 greatly reduced mean survival time in the 250g & 500g groups ($p \leq 0.0001$) compared to all other treatments. Both L and D were protective against 48/80, and D also protective against C+48/80, for absolute survival and mean survival time ($p \leq 0.0001$). Conclusions: Death due to 48/80 is age-dependent and mediated by H_1 receptors. L and D are protective by blocking HM release or its effects on peripheral H_1 receptors, respectively. The adverse effect of C (100% mortality increase in 250g rats, plus highly significant decreases in mean survival time in 250 & 500g rats) suggests that H_2 receptors mediate an important component of the cardiovascular response to stress which requires further evaluation.

5 HEMODYNAMIC CHANGES IN ENDOTOXIN SHOCK OF NEONATAL PIGLETS.
Andrew J. Griffin, Pui Kan Liao* and Dharmapuri Vidyasagar*. University of Illinois at Chicago, Illinois Masonic Medical Center, Department of Pediatrics, Chicago, IL 60657.

Acute endotoxin shock models in the adult animals have been studied far more extensively than newborn animals related in part to the difficulty in recording cardiac output and deriving resistance values. In this study, newborn piglets (3-12 days of age) were studied for acute hemodynamic changes for 4 hrs following IV injection of E.Coli lipopolyseccharide (LPS). Pulmonary blood flow was monitored by electromagnetic flow probe, pressures were recorded in the AO, PA, LA, and RA. Five animals received LPS only as the septic control (group I). The other five received IV indomethacin (IND) 5' following LPS (group II). All animals were anesthetized and ventilated. Changes in group I and II animals were analyzed at 0', 15', 1°, 2° and 4° post LPS by ANOVA. **Hemodynamics:** (1) LPS induced an immediate decrease in cardiac output (CO), and sharp rise of pulmonary artery pressure (PAP) reflecting a dramatic increase in pulmonary vascular resistance (PVR). (2) IND failed to block the increase in PVR and pulmonary hypertension effectively. (3) Aortic pressure (AOP) was initially maintained in both groups by an increase in the systemic vascular resistance (SVR), but hypotension developed after one hour post LPS in septic control animals. (4) IND transiently restored the CO and the AOP was maintained for 2 hrs post LPS in treated animals. CO fell and SVR then increased. Metabolic acidosis developed at 4 hrs post LPS in both groups. In contrast to adult pigs, hyperdynamic state was absent. **Conclusions:** IND transiently altered the hemodynamic effect of LPS in the early phase (up to 2 hrs) of endotoxemia. Late sequlae of endotoxemia were not prevented.

6 EVIDENCE FOR THE EXISTENCE OF BETA-ENDORPHIN IN THE HEART

Carl E. Hock, Lloyd J. Forman, Joseph Costabile and Diane K. Reibel. University of Medicine and Dentistry of New Jersey-SOM, Cooper Hospital/UMC, Camden, NJ 08103 and Thomas Jefferson University, Phila., PA 19107.

Recent reports suggest that circulating endogenous opiates may influence cardiac function. We have investigated the presence of beta-endorphin (BE) in the rat heart under both physiologic and pathophysiologic conditions. Rats were subjected to either abdominal aortic constriction (AC) or sham operation (SO). Four weeks following AC, cardiac hypertrophy was evidenced by significantly elevated ($p<0.001$) heart weight-to-body weight ratios. Using gel chromatography and radioimmunoassay, BE was detected in ventricular homogenates from both experimental groups. When expressed on a gram wet weight basis, there was no significant difference between groups (569±39 vs 581±53 pg/g wet wt, SO vs AC, respectively). However, the ratio of cardiac BE to its precursor, beta-lipotropin (BLPH), was significantly elevated for AC rats (1.69±0.06 vs 1.17±0.06, AC vs SO, respectively, $p<0.001$). The BE content of the heart was not reduced by buffer perfusion by the Langendorff procedure prior to assay. AC rats exhibited a significant elevation in plasma BE ($p<0.01$), however, the plasma BE/BLPH ratio was not altered. The data demonstrate both the presence of BE in the myocardium and an altered ratio of BE/BLPH during circulatory stress (i.e., hypertrophy). The ratio of BE/BLPH in the heart varies independently of that in the plasma in AC rats. The data suggests that BE of myocardial origin may participate directly in the pathophysiology of certain types of myocardial or circulatory dysfunction.

7 BURN SHOCK EXACERBATES AGE-RELATED MYOCARDIAL CONTRACTILE DYSFUNCTION. J.W.Horton, D.J.White*,C.F.Baxter*. UT Southwestern Medical Center, Dallas, TX 75235-9031

Left ventricular (LV) contractile function was assessed in young (YO, 7 days of age) and adult (AD, 5-6 months of age) isolated coronary perfused guinea pig hearts. Compared to AD control hearts (N=20), YO control hearts (N=20) showed significantly lower LV systolic pressure (LVP, 87±3 vs 71±2 mmHg, $p<0.05$), maximal rate of LVP rise (+dP/dt max, 1351±57 vs 1111±95 mmHg/sec, $p<0.05$) and fall (-dP/dt max, 1154±34 vs 1042±36 mmHg/sec, $p<0.05$) at a constant LV end-diastolic pressure and constant coronary flow rate. A 43±2% total body surface area (TBSA) 3rd degree burn (Walker model) produced a 24% mortality in AD while a 37± 1% TBSA in the YO group caused a 47% mortality. Compared to AD burn hearts (N=20), hearts from YO burned animals (N=17) generated significantly lower values for LVP (63±4 vs 56±2 mmHg, $p=0.05$) and +dP/dt max (1151±62 vs 860±89, $p=0.05$). Cardiac deficits in YO burned hearts were not overcome by increases in coronary flow rate. While increases in extracellular calcium concentration (from 1-8 mM) and isoproternol (from 1 to 30 ng) improved LVP and ±dP/dt max in a dose dependent manner in all burn hearts, cardiac performance was consistently less in the YO compared to AD hearts at each calcium and at each isoproterenol concentration. At the maximally effective isoproterenol dose (30 ng), LVP (104±9 vs 141±11), +dP/dt (2151±183 vs 2985±284) and -dP/dt (1730±162 vs 2240±119) were significantly lower in YO compared to AD burn hearts ($p<0.05$). Increased mortality and diminished functional responses to isoproterenol and calcium in YO compared to AD burned hearts indicate reduced contractile reserves in the young age group.

8 ERYTHROPOIESIS DURING ENDOTOXIN SHOCK. J. Hubbard. University of Delaware, School of Life and Health Sciences, Newark, DE. 19716.

Endotoxin (EX)-induced changes in erythropoiesis and the possible role of erythropoietin (EPO) were investigated in young swine with a sham-surgical control group (N=8) and a second group (N=8) receiving a bolus injection of 0.75 mg/kg E. coli EX. Anethetized animals were surgically prepared with arterial and venous catheters for obtaining blood samples prior to and at 30, 60, 120, 180, and 240 minutes following sham or EX injections. Mean arterial pressure (MAP) was monitored throughout the experiment. All blood samples were measured for hemoglobin (Hb), hematocrit (Hct), red cell count (RBCs), reticulocyte count (Ret.ct.), nucleated red blood cell count (NRBC), and EPO. Duplicate bone marrow aspirates were obtained before and at the end of the experiment for analysis of the myeloid/erythroid (M:E) ratio. The EX-shock group demonstrated a significant drop in MAP by 1-hour. An EX-mediated in-

crease in erythropoiesis was suggested by sustained, significant increases in Hb, H.c, PVCs, Reticl., and NRBC in the EX shock group, as compared to the control group. In addition, the M:E ratio of the marrow increased 4% after EX injection as compared to a 26% decrease in the control group. Since ischemia and hypoxia is known to be a effector of EPO release, blood gases were measured throughout the experiment. Arterial pH and PO2 demonstrated a significant decrease across time in the EX-shock group. The EPO, however, did not significantly change across time in the EX-shock group, as compared to the control group. These data suggest stimulated erythropoiesis in E. coli EX-shock but that this stimulus does not appear to be mediated by a hypoxia-stimulated increase in EPO.

9 **TUMOR NECROSIS FACTOR$_\alpha$ DECREASES VASCULAR CONTRACTION IN VITRO.** P. Kutsky. Dept. of Physiology, Texas College of Osteopathic Medicine, Fort Worth, Tx 76107.

Tumor necrosis factor$_\alpha$ (TNF$_\alpha$, cachectin) secreted by macrophages in response to endotoxin may be an important mediator in septic circulatory shock. Specific membrane receptors have been identified for TNF$_\alpha$ in both muscle and vascular endothelium. This study was conducted to evaluate the effect of TNF$_\alpha$ on vascular responsiveness in vitro. Rings from canine renal interlobar arteries were equliberated to a resting tension of 1.5 g in physiological buffer, pH 7.4. Each vessel was initially contracted with norepinephrine (NE) and a functional endothelium was subsequently verified by at least 50% relaxation with acetylcholine (10^{-5}M). Rings were washed repeatedly and recontracted with NE (5×10^{-6} - 1×10^{-7}M). After stabilization of the contraction, 3,400 U/ml of TNF$_\alpha$ were added to the bath. After a 10-15 min latency, the strength of contraction gradually decreased. By 30 min, TNF$_\alpha$-treated rings (n=19) had relaxed 38.95 $\pm$ 3.48% versus 2.42 $\pm$ 5.15 for controls (n=19). A similar TNF$_\alpha$ effect was observed in NE-contracted branches of the femoral artery and in PGF$_{2\alpha}$-contracted branches of the left anterior descending coronary artery. Repeated TNF$_\alpha$ responses could not be demonstrated in the same vessel despite frequent washings and re-equilibration. The lag in the TNF$_\alpha$ response suggests an indirect effect involving synthesis and/or release of a required secondary intermediate. The vasodilatory effect of TNF$_\alpha$ may be an important factor in the failure of peripheral vascular resistance to compensate appropriately during septic shock. (Supported by TCOM Organized Research).

10 **PROLONGED EXPOSURE OF VASCULAR TISSUE TO SMALL DOSES OF ENDOTOXIN IN VITRO RESULTS IN IMPAIRED CONTRACTILE FUNCTION.** T. McKenna* (Spon: J. Filkins). Naval Medical Research Institute, Bethesda, MD 20814.

This study characterized contractile responses by vascular tissue after prolonged treatment with low doses of endotoxin (Etx). Aortic rings isolated from rats were incubated 18 hr with Etx (1 to 100 ng/ml). Additional rings were incubated with 10 ng/ml Etx in the presence or absence of a functional endothelium (Endo), fetal calf serum (FCS, 10%), or Actinomycin-D (ActD, 25 uM) to examine the modulation of Etx influence by these agents. Isometric contractile responses by rings to norepinephrine (NE) were tested in an organ bath; ring contractile performance was expressed by integrating responses to NE over a dose range from 1 nM to 30 uM. N=8 to 12 replicates in each experiment.

Etx	Response	Endo	Response	FCS	Response	ActD	Response
Control (C)	4302±338[a]	C+Endo	3106±262	C+FCS	3485±213	C+ActD	4406±433
1 ng/ml	2260±386*	C-Endo	3825±379*	C-FCS	3644±243*	C-ActD	3946±303*
10 ng/ml	1367±247*	Etx+Endo	571±100*	Etx+FCS	1036±116*	Etx+ActD	4194±347*
100 ng/ml	751±170*	Etx-Endo	1314±194*	Etx-FCS	858±234*	Etx-ActD	726±111*

[a](mg tension/mg tissue vs. ln [NE] M) *P<.05 vs. Control or C + Endo, FCS, or ActD

These findings support conclusions that long-term exposure to small doses of Etx result in impaired vascular contractile function that does not require endothelial cells or serum factors for expression; in addition, because protein synthesis is necessary for suppression, a question remains whether the suppressive action of Etx is direct or via a mediator generated by Etx-stimulated vascular tissue.

11 THE EFFECT OF MODERATE HYPOTHERMIA ON MYOCARDIAL MORPHOLOGY AND METABOLISM DURING SEVERE HEMORRHAGIC SHOCK. D.Meyer*,J.Stout*,J.Horton,P.Walker*. UT Southwestern Medical Center, Dallas,TX 75235-9031

Previous studies show that severe hemorrhagic shock (HS) produces myocardial injury. This present study examined the effects of hypothermia (HYPO) on myocardial morphology (formation of hypercontraction lesions) and metabolism during HS. A total of 20 dogs were hemorrhaged to a mean arterial blood pressure of 30 mmHg, and divided into group 1 (body temperature (BT) 33°C, N=10) and group 2 (normothermic, NORMO, 38°C BT, N=10). After two hours HS, dogs were removed from pressure reservoir, received neither shed blood or fluid and were monitored until death. Myocardial morphology was examined by histologic methods, and lesions were quantitated by the point counting technique; myocardial ATP tissue content was measured by nuclear magnetic resonance spectroscopy. Compared to NORMO, HYPO significantly improved survival (1.47±.23 hrs vs 18.6±2.18 hrs, $p<0.05$). HYPO tended to reduce the percent of myocardium involved with hypercontraction injury (HYPO: 8.8±2.0, NORMO: 11.6±2.9), but this failed to achieve significance. It was of interest that hypercontraction injury was similar in all dogs despite a longer period of hypotensive shock in the HYPO dogs. Hypothermia in hemorrhagic shock preserved phosphocreatine levels (HYPO: 1.7±0.4; NORMO: 0.9±.3) while inorganic phosphate was lower in HYPO compared to NORMO HS (4.3±.3 vs 5.2±1.0). Our data suggests that the hypothermia-mediated decrease in metabolic rate and conservation of high-energy phosphate compounds may provide a protective effect in severe HS.

12 RELATIONSHIP OF CARDIAC WORK, BLOOD FLOW AND ENERGY STORES TO THE ONSET OF DECOMPENSATION DURING HEMORRHAGIC SHOCK(HS). F.J. Pearce. Univ. of Rochester Sch. Med. & Dent., Rochester, NY 14642.

Deterioration of the homeostatic mechanisms responsible for maintaining blood pressure after severe blood loss may be the result of either the failure of maintenance of cardiac output(CO) and/or of systemic peripheral resistance. This study evaluates the possible role of cardiac ischemia in precipitating the onset of decompensation. Pentobarbital- anesthetized Sprague-Dawley rats were studied using an isobaric model of hypovolemic shock (40 mm Hg). All measurements were taken just prior to bleeding and at 4 subsequent physiologic stages of HS which were defined on the basis of the shed blood volume(SBV); I) 50% of projected maximum SBV, II) peak SBV, III) and IV) after return of 20% and 75% of the SBV, respectively. Coronary flow(CF) and CO were measured using the microsphere reference flow method. The results follow:

	Control	I	II	III	IV
CI (ml/min * kg BW)	297 ± 40	103 ± 10	57 ±14	81 ± 6	91±14
SWI (g-m/kg BW)	1.23 ± 0.16	0.21±.03	0.10 ±.01	0.11±.01	0.12 ± .02
CF (ml/min * g wet)	3.7 ± 0.7	1.8 ± 0.5	3.8 ± 0.3	4.3 ± 0.2	3.5 ±0.4
ATP (µmol/GD)	21.6 ± 0.6	22.8 ± 1.4	21.0 ±0.5	18.4 ±0.6	16.7 ±0.5
CrP (µmol/GD)	19.9 ±1.8	32.6 ±3.4	26.9 ±1.8	28.5 ±3.2	13.4 ±3.3
Glycogen (µmo/GD)	129 ± 8	150 ±17	217 ± 46	253 ±30	164 ±49
G-6-P (µmol/GD)	1.4 ± 0.2	1.7 ± 0.5	2.3 ± 0.4	2.4 ± 0.5	3.8 ±1.8
Lactate (µmol/GD)	1.9 ± 0.2	3.9 ± 0.7	20.5 ± 5.0	20.1 ± 3.6	35.2 ±13.2

Since arterial PO_2 was unaltered throughout the protocol, these results show that oxygen delivery fell proportionately less than cardiac work. Normal and elevated ATP and CrP levels,respectively, in association with increased tissue lactate and glucose-6-phosphate levels and glycogen accumulation well into the decompensatory phase of HS indicate that cardiac ischemia is unlikely to contribute to the onset of decompensation.

13 CARDIAC DYSFUNCTION DURING HYPERDYNAMIC ENDOTOXEMIA OCCURS WITH NORMAL CARDIAC MORPHOLOGY. K. Sugi*, F.Terasaki*, L.D.Traber, D.N.Herndon D.L. Traber. University of Texas Medical Branch, and Shriners Burns Institute, Galveston, TX 77550.

Depressed myocardial contractility has been reported to occur during hyperdynamic (increased cardiac output reduced peripheral vascular resistance) endotoxemia. Derangements in cardiac histology and the myocardial contractility have been reported to occur in animal models of hypodynamic endotoxemia. Consequently, we studied cardiac histology in a hyperdynamic model to determine whether structural changes were responsible for myocardial dysfunction. The experiments were accomplished in 13 unanesthetized sheep which had been chronically prepared for measurement of cardiovascular function. Baseline data were collected in the unanesthetized state seven days after the last surgical procedure and the animals were then given 1.5 mcg/kg E.coli endotoxin (LPS). Six of the animals were sacrificed at 12 hours after the

administration of endotoxin and their hearts harvested for histological evaluation. The administration of endotoxin resulted in an increase in cardiac output which plateaued between 8 and 16 hr. During this time period several indices of left ventricular myocardial contractility (Emax, maximum dP/dt, ejection fraction, Vmax) were depressed below the baseline level. Hearts collected during this time period showed a normal histology. It is concluded that the depression of myocardial contractility which occurs during endotoxemia is not the result of anatomical derangements.

	CO	Emax	max dP/dt	EF	Vmax
baseline	5.7±0.4	5.6±0.4	1538±74	50±3	92±7
12 hrs post LPS	7.9±0.6*	4.4±0.5*	1274±91*	44±4*	67±7*

(HL34752)
*; p<0.05
(Dunnett's test)

14 PROLONGED DEPRESSION IN MICROVASCULAR BLOOD FLOW (BF) FOLLOWING HEMORRHAGE AND RESUSCITATION. P. Wang*, P.A. Wagner*, J.G. Hauptman, I.H. Chaudry. Department of Surgery, Michigan State University, East Lansing, MI 48824-1315.

We have used a laser doppler blood perfusion monitor (TSI Laserflo model 403A) to determine microvascular BF changes in various organs following hemorrhage and resuscitation. Following midline laparotomy and measurement of BF, blood volume and velocity, non-heparinized rats (n=18) were bled to and maintained at a mean BP of 40 mmHg until 40% of the shed blood volume was returned in the form of Ringer's lactate (RL). The rats were then resuscitated with 2 X the volume of maximum shed blood with RL. BF (mean±SE) in the liver, kidney and intestine following maximum bleed out was 37±2%, 17±2% and 17±4% of control, and following resuscitation it was 56±5%, 27±3% and 27±3% of control, respectively. The changes in red cell velocity followed the same trend as the changes in BF. Blood volume in the liver and intestine following maximum bleed out was 119±14% and 169±24%, and following resuscitation it was 148±12% and 157±23% of control respectively, indicating stasis in these organs. Even 3-5 days following resuscitation, BF in the liver, kidney and intestine remained markedly depressed despite the return of blood volume to prehemorrhage values. These results lead us to conclude that: 1) The progressive changes in microvascular BF following hemorrhage and resuscitation can be measured by using the laser doppler blood perfusion monitor, 2) a significant stasis occurs in the liver and intestine following hemorrhage despite resuscitation and, 3) resuscitation following hemorrhage with 2 X the volume of Ringer's lactate does not restore BF to organs in this non-heparinized model of hemorrhage (Supported by NIH GM39519).

15 ENDOTOXIN ALTERED MICROVASCULAR RESPONSES TO ADRENERGIC AND VASOPRESSIN (AVP) INFLUENCES. Carleton H. Baker, E. Truitt Sutton*, Zhong Zhou*. Dept. of Physiology and Biophysics, Univ. of South Florida, Tampa, FL 33612.

We demonstrated decreased microvascular sensitivity to norepinephrine during endotoxin shock (Circ. Shock 12:165, 1984). Vascular controls such as AVP and adrenergic nerves may also be altered. Reactivity of the left cremaster muscle microvessels of pentobarbital anesthetized Wistar rats was studied using videomicroscopy and videodensitometry. Femoral arterial pressure (Pm) was measured. Dose response curves of second and third order arteriolar diameters to topical AVP (10^{-6}M to 10^{-15}M) were determined in 10 rats. Frequency response curves of arteriolar diameters to sympathetic stimulations (1-16 Hz) were obtained in 10 rats. Arteriolar plasma velocities and mean transit times ($\bar{t}$) were determined from injections of FITC-albumin. E. coli endotoxin (3 mg/kg) was infused i.v. over a 1 hr. period. Pm and flow velocities progressively decreased with time post-endotoxin. FITC-albumin $\bar{t}$ increased post-endotoxin. The arteriolar threshold dose for constriction by AVP decreased significantly from 10^{-9}M at control to 10^{-14}M after endotoxin. The frequency-diameter curves shifted significantly to the right post-endotoxin indicating reduced responsiveness to adrenergic influences. At 16 Hz the A_3 arteriolar diameter at control averaged 55 ± 5% of resting diameter, 30 min after endotoxin averaged 85 ± 3% and at 90 min averaged 87 ± 3%. Reduced sensitivity to norepinephrine and responsiveness to adrenergic nerve stimulation suggest unmasking the responsiveness to AVP or increases in the sensitivity of AVP receptors due to changes in the balance of adrenergic and V_1 receptor interactions. (Supported by USPHS grant HL-33840)

16 TUMOR NECROSIS FACTOR DOES NOT MEDIATE DECREASES IN RENAL AND INTESTINAL MICROVASCULAR BLOOD FLOW DURING BACTEREMIA IN THE RAT. F.Bentley, H.Cryer, L.Unger, D. Livingston, G.Sonnenfeld, R. Garrison. Univ. of Louisville, Louisville, KY. 40292.

We have previously shown that acute high cardiac output E. coli bacteremia causes significant reductions in renal and small intestine microvascular blood flow. To determine if TNF causes similar responses we measured microvascular blood flow in sequential arteriolar branches leading to a glomerulous in the kidney (chronic hydronephrotic kidney preparation) and a villus in the small intestine to document microvascular blood flow to the functional unit of each respective organ in separate groups of rats for two hours after intravenous administration of either 0.1 mg/kg human TNF alpha (Genentech) in 1 cc 0.5% bovine serum albumin (BSA) or BSA alone (control) by in vivo videomicroscopy and optical Doppler velocimetry in decerebrate male Sprague-Dawley rats. Data expressed as percent (%) of baseline values of cardiac output (CO), mean arterial pressure (MAP), and microvascular blood flow (Flow) at 2 hours were compared to previous data from E. coli bacteremia (E. coli):

	KIDNEY			SMALL INTESTINE		
	Control(n=5)	TNF(n=5)	E.coli(n=5)	Control(n=6)	TNF(n=7)	E.coli(n=5)
CO	96±5%	84±9%	127±4%*	103±6%	91±4%	115±13%
MAP	102±1%	97±4%	100±4%	103±3%	96±7%	100±3%
Flow	105±5%	101±6%	57±11%*	92±3%	91±11%	43±6%*

* = $p<.05$ by ANOVA + Bonferroni t test, (E. coli vs. TNF)

These data indicate that unlike E. coli bacteremia, 0.1 mg/kg of TNF does not alter renal or small intestine microvascular blood flow in the rat.

17 MACROPHAGE-MEDIATED ENHANCEMENT OF SYSTEMIC HOST-DEFENSE. S. Bernard* and G. D. Niehaus* (SPON: L. Traber), Northeastern Ohio Universities College of Medicine, Rootstown, Ohio 44272. (Funded by United Way of Stark County)

The rate at which the Mononuclear Phagocyte System (MPS) removes bacteria from the circulation is a function of both macrophage number and phagocytic activity. This study investigated mechanisms of MPS modulation by evaluating the hypothesis that macrophage activation stimulates proliferation, sequestration and activation of monocytes in the major MPS organs. Rat bacterial clearance capacity was measured for 5 days following macrophage activation (glucan) or saline infusion (control).

TABLE. Effect of Macrophage Activation on systemic host-defense. Organ weights and culturable bacteria were measured 7 minutes after E. coli infusion (10^9/ 100 g). Mean data for glucan challenged rats is presented as % change from time-matched controls.

DAYS POST-GLUCAN CHALLENGE	1	2	3	4	5
BLOOD MONONUCLEAR COUNT	24	26	87	61	-
BLOOD COLONY FORMING UNITS	84	64	41	75	-
LIVER WEIGHT	98	93	90	110	102
LIVER COLONY FORMING UNITS	119	113	117	81	41
LUNG WEIGHT	100	146	110	109	108
LUNG COLONY FORMING UNITS	97	53	89	48	108
SPLEEN WEIGHT	116	158	210	255	250
SPLEEN COLONY FORMING UNITS	162	63	47	28	27

Monocyte sequestration is suggested by the decreased blood monocytes and increased MPS organ weights. The inverse relationship between organ weight and culturable blood and organ bacteria suggests increased uptake and killing of bacteria. It appears that enhanced function is uniquely regulated within each organ, with activation being transient in lung, delayed in liver and progressive in spleen.

18 THE EFFECT OF SYSTEMIC ENDOTOXIN ON SKELETAL MUSCLE VASCULAR CONDUCTANCE DURING HIGH AND LOW ADRENERGIC TONE. R. F. Bond, C. Scott*, J. C. Clevenger*, C. H. Bond* and F. L. Abel. University of South Carolina School of Medicine, Columbia, SC 29208.

The objective of this study was to determine the role of adrenergic tone on the peripheral vascular decompensation reported to occur during systemic endotoxemia. A constant-flow double-canine gracilis muscle(GM) preparation allowed one GM to serve as an innervated control(GMc) for the contralateral denervated muscle(GMe). Group I(n=9): inherent vascular tone; Group II(n=7): adrenergic tone elevated by bilateral common carotid artery occlusion. GMc Group I and II vascular conductances were significantly different at .0636 ± .005 and .0485 ± .004 ml/min/100gm/mmHg, respectively. GM denervation had no significant effect on Group I conductance suggesting a low level of intrinsic adrenergic tone; however, denervation did increase the vascular

conductance by more than 30% from .0485 ± .004 to .0638 ± .008 ml/min/100gm/mmHg in Group II. A 2 mg/kg dose of endotoxin was infused i.v. over 30 min and data collected over an additional 60 min. The endotoxin caused a decrease in MAP from 129 ± 5 to 73 ± 6 mmHg in Group I; and, from 177 ± 16 to 92 ± 14 mmHg in Group II. Both the GMc and GMe Group I GMs showed an initial increase in conductance to 115 ± 9 and 117 ± 8%, respectively, at 5 min followed by a reduction to 82 ± 9 and 101 ± 10% at 60 min. Group II showed a significantly increased conductance following denervation to 125% which increased insignificantly to 135% at 60 min, while conductances either remained at about 100% or decreased slightly in the innervated Group II GMc. The data suggests that the baseline level of vascular tone is an important factor when evaluating the effect of systemic endotoxemia on the skeletal muscle peripheral vasculature. [Supported by grants from the SC Heart Assoc and USC BRSG.]

19 **ALTERATIONS IN RESPONSE TO GUANINE NUCLEOTIDES IN ENDOTOXIN TOLERANCE.** K. Coffee*, W. Wise, P. Halushka, J. Cook. Medical University of South Carolina, Charleston, SC 29425

Endotoxin (LPS) tolerance (TOL), a phenomenon induced by repeated administration of sublethal doses of endotoxin, is characterized by a refractory response to otherwise lethal LPS doses. Macrophages (MØ) from TOL rats exhibit decreased synthesis of arachidonic acid (AA) metabolites in response to LPS. Data suggest that guanine nucleotide binding (G) protein(s) mediate LPS induced AA metabolism. Nonhydrolyzable analogs of GTP and GDP modulate GTP binding protein activity. GTP-[γ-S] activates whereas GDP-[β-S] inhibits GTP binding proteins. This study assessed LPS (50 μg/ml) induced stimulation of thromboxane $(Tx)B_2$ in normal (CON) and TOL rat peritoneal MØ. In CON MØ treated with GTP-[γ-S], LPS induced TxB_2 formation was significantly increased at early time points compared to LPS whereas LPS induced TxB_2 formation in CON cells treated with GDP-[β-S] was significantly lower compared to LPS. In TOL cells, neither GTP-[γ-S] nor GDP-[β-S] had any effect on TxB_2 synthesis compared to LPS.

TIME (hr)		0.5	1.0	2.0	3.0	4.0
CONTROL	BASAL	4.3±0.4‡	4.8±0.4‡	7.0±0.5‡	5.5±0.4‡	5.0±0.5‡
TxB_2 (ng/ml)	LPS	9.1±2.3	12.3±1.8	18.2±1.7	20.1±1.6	18.9±1.5
	GTP-[γ-S]-LPS	12.3±0.2*	14.5±0.5	18.2±1.1	21.5±0.7	20.8±1.5
	GDP-[β-S]-LPS	8.9±0.3	10.8±0.4	14.8±0.7*	13.5±0.6*	17.2±0.7
TOLERANT†	BASAL	N.D.	N.D.	0.4±0.08‡	0.4±0.03‡	0.4±0.05‡
TxB_2 (ng/m)l	LPS	N.D.	N.D.	0.7±0.09	1.9±0.1	3.0±0.1
	GTP-[γ-S]-LPS	N.D.	N.D.	0.7±0.08	1.9±0.2	2.6±0.2
	GDP-[β-S]-LPS	N.D.	N.D.	0.7±0.06	1.7±0.2	3.1±0.3

*p<0.05 vs CON LPS; †p<0.05 vs CON; ‡p<0.05 vs LPS; N.D.=Nondetectable. Data are Mean±SEM.

These data suggest that (1) G proteins mediate LPS signal transduction and AA metabolism in MØ and (2) that depressed G protein - post receptor coupling may mediate LPS tolerance. (Supported by NIH GM27673).

20 HISTAMINE RELEASE IN CLINICAL SEPTIC SHOCK: CAUSED BY SEPSIS, INTENSIVE CARE TREATMENT, SURGERY OR THE PRIMARY DISEASE? W. Dietz*, W. Lorenz, E. Neugebauer, B. Stinner*, J. Sattler*, M. Rothmund*, Center of Operative Medicine I, University Marburg, D-3550 Marburg F.R.G.

The discrepancy between study results on sepsis and septic shock in human beings and animals can be explained by the primary disease or the therapeutic maneuvers, whereas the animals are made ill without any treatment. In a prospective cross-sectional study on 20 patients with septic shock (VA-inclusion criteria Coop.Study 209, 1987) and 20 control patients with limb injuries we have investigated if the elevated plasma histamine levels are caused by sepsis or were the result of therapy, surgery and the primary disease. A causality analysis was therefore performed by comparison of 19 variables in both groups with the Mann-Whitney-Test (Koch/Dale-Criteria I+II), regression- and correlation analysis in the septic patients as well as through the use of the 9 criteria of Hill (Livingstone, 1962). At the beginning of the septic shock, the plasma histamine levels were elevated (0.50 (0.15 - 25.8) ng/ml, $\tilde{x}$ (range)) in comparison to controls (0.17 (0.06 - 0.90) ng/ml, $\tilde{x}$ (range)) ($p < 0.001$). The statistical comparison of the many variables obtained from the test- and control groups were significant in nearly all cases. In the correlation analysis only fever and histamine levels showed a strong correlation. Using the Hill criteria the degree of temperature increase and plasma histamine levels were correlated. In addition the plasma histamine levels of patients who recovered were reduced. This analysis demonstrate that histamine release was caused by sepsis. There seems to be no causal connection between the intensive care therapy or the primary disease with increased plasma histamine levels.

21 EFFECT OF A PLATELET ACTIVATING FACTOR (PAF) ANTAGONIST (SRI64,688) ON PLASMA THROMBOXANE B_2 (TxB_2) CONCENTRATION, MEAN PULMONARY ARTERY PRESSURE (PAP) AND MESENTERIC PERFUSION (Qsma) IN PORCINE ENDOTOXIC SHOCK. M. Fink*, T. Baum, H. Wang, H. Rothschild. Univ of Mass Med Ctr, Worcester, MA 01655.

Two groups of pigs were infused with E. coli LPS (150 ug/kg over 20 min) and continuously resuscitated with saline (1.2 ml/kg·min). Group I (n=7) were vehicle-treated controls. Group II (n=6) were pretreated (t= -20 min) with SRI64,688 (5 mg/kg). Gut mucosal hydrogen ion concentration, [H+], was determined tonometrically. Except for immunoreactive TxB_2 data, results are expressed as mean (±SE) percent changes from control. * = $p < .05$ vs control, # = $p < .05$ vs time-matched value in Group I. CI = cardiac index. MAP = mean arterial pressure.

Time	20 min		80 min	
Group	I	II	I	II
CI (%)	-23± 8*	-23± 1*	-6±11	-1± 6
MAP (%)	12± 3*	11± 4*	-38± 4*	-39± 5*
PAP (%)	197±30*	129±28*#	93±22*	48±14#
Qsma (%)	-36±10*	-27±10*	-26±10*	-36± 5*
[H+] (%)	17± 3	20± 4	66±16*	94±37*
TxB_2 (ng/ml)	5.7±1.2*	2.8±.2*#	5.5±1.1*	3.8±.9*

CONCLUSION: SRI64,688 blunted the pulmonary hypertensive and TxB_2 response to LPS but failed to improve systemic or mesenteric hemodynamics. PAF is a mediator of LPS-induced thromboxane release and pulmonary hypertension. Supported by NIH grant 1 R29 GM37631-01A1 and a grant from Sandoz Research Institute.

22 CHARACTERIZATION OF A23187- AND MELITTIN-STIMULATED ARACHIDONIC ACID RELEASE FROM MICROVESSEL ENDOTHELIAL CELLS *IN VITRO* : A MODEL FOR ENDOTOXIN-MEDIATED MICROVASCULAR INJURY. J. T. Flynn. Thomas Jefferson University, Philadelphia, PA 19107.

Bacterial endotoxins and lipid A stimulate arachidonic acid (AA) metabolism in large vessel endothelial cells. The present study characterizes ^{14}C AA incorporation into rabbit adipose capillary endothelial (RACE) cells and examines the source of AA released in response to A23187 and melittin (MEL), a phospholipase activator. RACE cells were harvested via a collagenase digestion and purified on a 45% Percoll gradient. Cells were incubated for 20 hrs. in medium containing 1 μCi of ^{14}C labeled AA. The cells were washed, and stimulated in medium containing saline vehicle, ethanol vehicle, 10 μM A23187, 5 μg/ml MEL, or 50 μg/ml MEL. After 30 min. of incubation at 37°C, cellular lipids were extracted and the amounts of ^{14}C associated with specific lipid fractions were determined by TLC and liquid scintillation spectroscopy. Control group cells incubated with saline (n=17) had 38.5±2.4%, 3.8±0.9%, 7.1±0.9%, and 50.6±2.2% of the label associated with phospholipids (PL), free fatty acids (FFA), diglycerides (DI), and triglycerides (TRI) respectively. Treatment of the cells with 0.5% ethanol significantly decreased the AA content of DI and TRI, but not PL . A similar situation was seen in cells treated with 10 μM A23187 using ethanol as the vehicle. No significant effect of the A23187 treatment could be discerned above the effect of the ethanol. Cells treated with 5 μg/ml MEL resulted in a significant increase in the cellular FFA content. There was a concurrent significant decrease in DI, but no change in PL . Fifty μg/ml MEL resulted in a 30% increase in cellular FFA and a significant decrease in the PL fraction. A significant decrease in the amount of labeled DI was also observed with the high dose of MEL. These data demonstrate that microvascular endothelial cells incorporate labeled AA into specific cellular lipids and that specific stimuli can release the label in a dose dependent manner. This model can now be used to determine the mechanism of endotoxin- and lipid A-mediated AA release in primary cultures of microvascular endothelium. Supported by GM 28023.

23 CARDIOPULMONARY EFFECTS OF INTERLUKIN-2 AND THE ROLE OF CYCLOOXYGENASE IN SHEEP R. Gunther, E. Morse*, G. Jesmok* and K. Hughes*. Dept. of Surgery, University of California, Davis, CA 95817 and Cetus Corp., Emeryville, CA 94608

Recombinant interleukin-2 (rIL-2) has shown promise in the treatment of patients with advanced cancer. A major complication in the clinical use of rIL-2 is the cardiopulmonary effects which result in hypotension and systemic and pulmonary edema. In previous studies we demonstrated that steroids could block these changes in sheep. We did the following study to ascertain if the cyclooxygenase metabolites of arachidonic acid are central to the acute rIL-2 induced cardiopulmonary changes. Six adult female sheep were prepared with lung lymph fistulas and cardiovascular catheters. Sheep were given either rIL-2,

100μg/kg, or rIL-2 plus the cyclooxygenase inhibitor ibuprofen (IBU), 12.5 mg/kg. Results are given as mean ± SEM. Cardiovascular variables were the same with or without IBU treatment. Core body temperature was unchanged with IBU, 39.2 ± 0.1°C, but increased from 39.3 ± 0.1° C to a maximum of 40.4 ± 0.2° C with rIL-2 alone. IBU did not block the rise in CO, 6.5 ± 0.3 to 7.8 ± 0.5 L/min, nor the increase in lymph flow, 7.3 ± 1.1 to 15.5 ± 3.3 ml/hr. Except for BT, these results indicate that the acute effects of rIL-2 are not predominantly related to cyclooxygenase metabolism of arachidonic acid but suggest alternate metabolism via the lipoxygenase pathway.

24 HUMAN NEUTROPHILS EXPOSED TO TUMOR NECROSIS FACTOR (TNF) OR PHORBOL-12-MYRISTATE-13-ACETATE (PMA) PRODUCE SUPEROXIDE BUT NOT HYDROXYL RADICAL. Steven A. Hamburger and Paul B. McCay*. Oklahoma Medical Research Foundation, Oklahoma City, OK 73104.

We determined the type, intensity and duration of oxygen-centered free radicals produced by human neutrophils (PMN; 10^6/ml) exposed to various concentrations of PMA or TNF. Hydroxyl or superoxide radicals were trapped with DMPO (100 mM) forming DMPO-OH and DMPO-OOH, respectively. The DMPO-radical adducts were measured with an electron paramagnetic resonance spectrometer at 6 min intervals for 1 hour. PMN exposed to PMA (0.06-6 μg/ml) produced DMPO-OOH and DMPO-OH in a concentration-dependent fashion. Superoxide dismutase (SOD; 10 μg/ml) and/or catalase (10 μg/ml) partially inhibited the appearance of both adducts, while neither desferal (0.1 mM) nor sodium azide (0.2 mM) had any effect. However, only the DMPO-OH adduct was detected after PMN were exposed to PMA (0.01 μg/ml) or TNF (0.1-10 nM). At these lower concentrations of PMA and TNF, SOD completely inhibited the appearance of these DMPO-OH adducts, while neither catalase nor sodium azide had anv effect. PMN exposed to ethanol and PMA (0.01-6 μg/ml) did not produce a 1-hydroxyethyl adduct, which is trapped by DMPO when hydroxyl radical attacks ethanol. No DMPO-radical adducts were detected at any time with unstimulated PMN. Although metabolism of superoxide radical, hydrogen peroxide or hypochlorous acid can produce oxygen-centered free radicals, these compounds did not contribute to the production of DMPO-OH adduct by PMN. This adduct may be formed by DMPO-OOH adduct degradation. Therefore, it appears that human neutrophils exposed to PMA or TNF produce superoxide but not hydroxyl radical. (Supported by NIH Grants GM36512 and GM08237).

25 EFFECT OF VITAMIN A ON THE SYNTHESIS OF LEUKOTRIENE C_4 INDUCED BY ENDOTOXIN N.Ishikawa, H.Suzuki, M.Onda, K.Yamada, N.Tanaka, K.Egami, T.Tajiri, K.Furukawa, M.Toba, T.Ando, T.Saito, T.Kobayashi, Y.Kanda and Y.Yoshino.The 1st Dept. of Surg. & The 2nd Dept. of Biochem. Nippon Medical School,1-1-5, Sendagi, Bunkyo-ku, Tokyo 113, Japan.

This study is designed to investigate the biological activity of vitamin A and leukotriene C_4 production in the inflammation of the tissue slices treated by endotoxin using vitamin A deficient rats. The rat organs used for this experiment were liver, kidney and intestine. (Material) Five weeks germ free rats fed by vitamin A deficient diet were used. (Results) Vitamin A contents in the organ tissues from normal rats were decreased by the endotoxin treatment; Liver tissue 72.7±14.4 to 24.8±1.9μg/g, Kidney tissue 0.23±0.07 to 0.09±0.04μg/g, Intestine tissue 0.35±0.16 to 0.19±0.1μg/g. Leukotriene C_4 production was induced soon after the endotoxin treatment of the organ tissues from vitamin A deficient rats ; Liver tissue 12.4±0.08ng/g, Kidney tissue 29.2±14.7ng/g, Intestine tissue 22.2±12.0ng/g. The pretreatment of the organ tissues from vitamin A deficient rats with vitamin A or vitamin A acid suppressed the production of leukotriene C_4 induced by endotoxin; Liver tissue 12.4±0.08 to 3.95±0.63ng/g, Kidney tissue 29.2±14.7 to 6.15±1.7ng/g, Intestine tissue 22.2±12.0 to9.5±2.2ng/g. (Conclusion) These results suggested that endotoxin inducing cell injury in the organ tissue can be protected by vitamin A administration.

26 AGE-RELATED DIFFERENCES IN THE SOMATOSTATIN (SRIH) RESPONSE TO ENDOTOXICOSIS IN RATS. L. Witek-Janusek, M.R. Yelich, J.K. Ratmeyer* and D.M. Umporowicz*. Loyola Univ. Med. Center, Dept. of Physiology, Stritch School of Medicine, Maywood, IL 60153

The 10 day old rat is more sensitive to endotoxin (E) induced glucose dyshomeostasis and lethality than the 28 day old rat. Since SRIH affects secretion of glucoregulatory hormones, alterations in its levels may relate to this developmental difference in sensitivity to E. This study determined plasma levels of somatostatin-like immunoreactivity (SLI) in fed, 10 and 28 day old rats injected ip with saline (S) or an LD_{90} dose of S. enteritidis E (0.2 mg/kg, 10 day; 30 mg/kg, 28 day). Trunk blood was collected hourly for 4 hr after S or E. Plasma levels of SLI, glucose and lactate were measured. SLI results are shown below as mean ± SE; pg/ml:

GROUP	Time->	0 hr	1 hr	2 hr	3 hr	4 hr
S 10 day		74 ± 3	58 ± 8	64 ± 10	56 ± 13	51 ± 8
E 10 day		--	54 ± 6	71 ± 8	102 ± 9[a]	90 ± 7[a]
S 28 day		50 ± 6	36 ± 6	36 ± 2	60 ± 5	66 ± 8
E 28 day		--	64 ± 12	84 ± 8[b]	143 ± 13[b]	159 ± 17[b]

a=p ≤ 0.05 (S vs E, 10 day); b=p ≤ 0.05 (S vs E, 28 day) N=4-11/group

At 4 hr, all E rats were hypoglycemic (< 69 mg/dl); lactate levels were elevated only in 10 day E rats (1 ± 0.1 vs 3 ± 0.3 mM; p≤0.05). SLI levels increased earlier and to a greater magnitude in 28 day E rats than in 10 day E rats. This age-related difference in the SLI repsonse may play a role in the increased sensitivity of the immature rat to endotoxin. (Supported by NIH HL31163 and DK36044)

27 CHANGES IN PLASMA CATECHOLAMINES DURING 6 HR INFUSION OF LOW-DOSE ENDOTOXIN (ET) IN CONSCIOUS RATS. S.B.Jones, M.Scannell*, R.Tijunelis* and L. Vassmer*, Loyola Univ. Med. Center, Maywood, IL 60153.

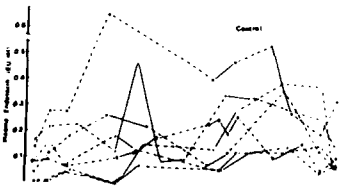
Bolus endotoxin increases plasma catecholamines in conscious rats in a pattern of early rapid increase and decline of epinephrine (E) as well as in early and sustained elevation of norepinephrine (NE). The present study evaluated the effect of continuous ET infusion on plasma E, NE heart rate and blood pressure. Fasted male rats (350g) were infused with saline with or without ET (S. enteritidis, 4 mg/kg,1.0 ml vol.) over 6 hrs. Rats were surgically prepared with arterial and venous cannulae the day before and fasted overnight. Survival was 60% (N=13) in ET rats. E and NE levels in multiple samples from the same rats during ET infusions (N=5) are:

Infusion (min)	0	30	90	180	240	360
NE (pg/ml plasma)	155±33*	207±41	1,014±238	607±166	1,026±119	1,288±159
E (pg/ml plasma)	174±64	267±124	1,247±280	566±149	769±117	1,045±128

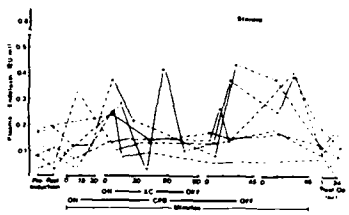
(*=Mean ±SEM). E and NE levels in saline rats (not shown) did not change over time. Maximal hypotension occurred with ET infusion at 80 min (88±7 in ET vs 114±4 mmHg in saline) but returned to control (110±5 mm Hg) by 130 min. Heart rate increased steadily with infusion and was 500±15 bpm in ET rats compared to 406±23 bpm in saline rats at 6 hrs of infusion. Changes in plasma E and NE appear biphasic, initially increasing with maximal hypotension but later increasing to equal magnitude but with normal blood pressure. Decreased NE at 180 min and further increases in both NE and E at 240 and 360 min are in contrast to plasma levels observed with bolus ET treatment. These results suggest that elevations in plasma E and NE may be due to factors other than blood pressure. Supported by HL 31163.

28 GASTROINTESTINAL ENDOTOXIN (EXT) TRANSLOCATION DURING CARDIOPULMONARY BYPASS (CPB): EFFECT OF METHYLPREDNISOLONE. M. Karlstad, S. Patteson*, J. Guszcza*, J. Langdon* and J. Chesney*. Dept. of Anesth., Univ. of Tenn. Med. Ctn., Knoxville, TN 37920.

This study investigated whether prophylactic administration of methylprednisolone sodium succinate (MPSS) could prevent an increase in plasma ETX levels during CPB. Studies have shown that endotoxemia due to EXT translocation in heat-stress and mesenteric artery occlusion shock is reduced by MPSS. Adult patients undergoing CPB were studied. Blood samples were collected pre- and post-induction, during and after CPB, and 1 and 24 hr post-op. Plasma EXT was assayed by chromogenic Limulus ameobycte lysate. The figure shows an intraoperative increase in plasma [ETX] that occurred primarily after initiation of CPB and removal of



the aortic cross-clamp (XC) in control and steroid patients. ETX at 1 and 24 hrs post-op was lower than the peak intraoperative levels and approached the pre-induction level in both groups. The pump prime contained ETX at or below the pre- or post-induction level. MPSS did not prevent endotoxemia during CPB. The loss of normal gut mucosal barrier function during CPB may result in endotoxemia and/or bacterial translocation, either of which could initiate or contribute to post-operative complications.



29 MYOCARDIAL DYSFUNCTION DURING EARLY NORMOTENSIVE ENDOTOXICOSIS IN GUINEA PIGS IS UNALTERED BY LEUKOTRIENE ANTAGONIST, LY171883. R.S. Keller, R.S. Watt, H.R. Adams, and J.L. Parker. Dalton Research Center and Dept. of Veterinary Biomedical Sciences, Univ. of Missouri, Columbia, MO 65211.

Isolated hearts were used to assess potential myocardial protective actions of the leukotriene antagonist, LY171883, 1-[2-Hydroxy-3-propyl-4-[4-(1H-tetrazol-5-yl) butoxy]phenyl]ethanone (LY), in early normotensive endotoxicosis. LY was administered as an iv bolus of either 8 mg/kg followed by a constant infusion of 8 mg/kg/hr (LY8)(n=5), 4 mg/kg followed by a constant infusion of 4 mg/kg/hr (LY4)(n=4), or equivalent volume of .5 M sodium bicarbonate solution (VEH)(n=5), 10 minutes prior to ip injection of 1 mg/kg purified *E. coli* endotoxin (ET). Hearts were isolated 4 hour post endotoxin injection for assessment of intrinsic myocardial function. 100% of ET animals receiving LY8 died within 4 hours, while only 20% receiving VEH and 0% receiving LY4 died. ET produced hypothermia which was unaltered by LY8 or LY4 treatment. Importantly, ET produced significant myocardial dysfunction and reduced left ventricular function curves which were not prevented by treatment with LY4. For example, left ventricular systolic pressure at equivalent preload averaged 86±8 and 87±11 respectively for control hearts treated with VEH and LY4; while values from ET animals averaged 49±6 and 56±10. Reduced inotropic responses to increasing Ca^{2+} concentrations (1-8 mM) in hearts from ET animals was not prevented by LY4. We conclude that LY4 does not prevent intrinsic myocardial dysfunction during early normotensive endotoxicosis in the guinea pig. Also, the data suggest a possible toxic interaction between LY8 and pathophysiologic mechanisms activated during gram-negative endotoxemia in the guinea pig model. (Supported by NIH HL36079 and HL01169).

30 LETHALITY AND ALTERED MACROPHAGE (MØ) CYTOKINE PRODUCTION FOLLOWING SEPSIS IN ENDOTOXIN-TOLERANT MICE. J.M. Kisala*, A. Ayala*, M.M. Perrin*, R.N. Stephan* and I.H. Chaudry. Department of Surgery, Michigan St. Univ., East Lansing, MI 48824.

The C3H/HeJ mouse strain is known to be resistant to many of the in vivo and in vitro effects of endotoxin (LPS), including lethality and MØ production of IL-1 and TNF-alpha. To determine whether such animals were less susceptible to sepsis, endotoxin-tolerant C3H/HeJ mice and endotoxin-responsive C57BL/6J mice were subjected to sepsis by cecal ligation and puncture (CLP). No difference was observed between these two strains in either early or late mortality (n=25/group). Since LPS is known to stimulate the production of IL-1 and TNF by MØ from LPS-intolerant mice in vitro, we elected to examine the capacity of peritoneal MØ (pMØ) obtained from LPS-tolerant C3H/HeJ septic mice to produce these cytokines. pMØ harvested 24 h after CLP or sham laparotomy (n=10/group) were incubated with and without LPS, and supernatants assayed for IL-1 (D10.G4.1 cell proliferation assay) and TNF (WEHI 164 clone 13 cytotoxicity assay). IL-1 production (units/10^6 cells, mean±SEM) by pMØ was increased in septic mice vs. controls both in the presence (1.74±0.24 vs. 0.70±0.10, $p<0.05$) and absence (1.57±0.27 vs. 0.04±0.02, $p<0.01$) of LPS. TNF levels were not altered. Blood was also obtained for endotoxin determination (limulus amebocyte lysate assay). Serum LPS levels were increased by a factor >10 in the CLP group vs. sham controls ($p<0.05$). These results suggest that pMØ obtained from endotoxin-tolerant C3H/HeJ septic mice undergo changes which allow them to produce IL-1 in the presence or absence of LPS in vitro. Whether or not these factors contribute to lethality remains to be determined (Supported by NIH GM 37127).

31 PERITONEAL MACROPHAGE SUPERNATANTS ALTER HEPATOCYTE ACUTE PHASE PROTEIN SYNTHESIS IN VITRO. P.Kispert* T.Billiar* R.Curran* R.Simmons* (Spon: T.Lysz) Univ. of Pittsburgh, Pittsburgh, PA 15261

Control of hepatocyte (HC) synthesis of certain proteins may be regulated by adjacent macrophages. We have shown that untreated rat kupffer cells increased HC protein synthesis and if triggered by LPS profoundly inhibit protein synthesis in coculture. We studied the effects of unelicited rat peritoneal macrophage (MØ) supernatants (SUP) conditioned with LPS on the synthesis of two hepatic acute phase proteins (APP). Albumin (ALB) and fibrinogen (FIB) synthesis by cultured rat HCs was measured using an immunoblotting technique. HC were treated with 1,5, and 10% MØ SUP. At 0,1,2, and 3 days samples of HC SUP were assayed for fibrinogen and albumin. The results are below:

	DAY					DAY			
ALBUMIN	0	1	2	3	FIBRINOGEN	0	1	2	3
Control	1.4±.4	-	15±3	23±3	Control	1.6±.6	5.2±2	10±1	12±3
MØ SUP (10%)					MØ SUP (10%)				
+ LPS	2.0±.6	-	34±12	30±3	+ LPS	2.2±.6	30±9	58±28	86±12
- LPS	2.0±.8	-	76±6	85±6	- LPS	2.6±1	25±4	32±6	27±8

(Results expresed as mcg/ml; mean ± S.D.)

Control HC showed an increase in FIB and ALB synthesis from day 0 to 3. MØ SUP (+LPS) caused a slight increase in ALB synthesis but caused a 7 fold increase in FIB sysnthesis by day 3. HCs treated with MØ SUP (-LPS) produced a 3.7 fold increase in ALB in a 2.2 fold increase in FIB synethesis. This suggests cytokines modulate synthesis of APP. Unstimulated MØs produce a product that enhances ALB synthesis while LPS treatment releases cytokines that strongly enhanced FIB synthesis but have lesser effect on ALB synthesis.

32 **EFFECT OF ENDOTOXIN (LPS) ON VASCULAR PERMEABILITY IN ESSENTIAL FATTY ACID DEFICIENT (EFAD) RATS.** E. Li*, J. Cook, K. Spicer*, W. Wise and P. Halushka, Medical University of South Carolina, Charleston, SC 29425.

Resistance to LPS in EFAD rats may be associated with reduced synthesis of certain eicosanoids. Since LPS causes changes in vascular permeability, its effect on changes in hematocrit (HCT) and mesenteric (GI) localization of ^{99m}Tc HSA and ^{99m}Tc RBC were assessed in EFAD rats. Gamma-camera imaging of heart (H) and mid GI regions generated time-activity curves for baseline and 5-35 min. after *Salmonella enteritidis* LPS (10 mg/kg). Slopes of GI/H ^{99m}Tc HSA activity provided a permeability index.

	CON	CON+LPS	EFAD	EFAD+LPS
Permeability Index (^{99m}Tc HSA)[a]	**0.8 ± 0.6 (6)†**	**4.9 ± 1.7 (7)**	**0.8 ± 0.2 (7)**	**1.2 ± 0.6 (7)***
HCT%[b]	**41 ± 3 (3)†**	**54 ± 1 (5)**	**44 ± 1 (4)**	**47 ± 2 (9)***

[a]GI/H x 10^{-3}/min, [b]HCT 30 min Post-LPS or VEH, †*P<0.05 vs. CON + LPS, ( ) = N

In contrast to ^{99m}Tc HSA, GI localization of ^{99m}Tc RBC was not changed by LPS in control or EFAD rats. These data suggest that EFAD rats are resistant to LPS induced hemoconcentration and permeability. Leukotrienes (LTs) have been implicated as mediators of increased vascular permeability in LPS shock. Since LTC_5 formation may be increased in EFA deficiency, we sought to determine its effect on permeability compared to LTC_4. Infusion of LTC_4 (4 µg/kg/min) in normal rats induced a rise in HCT from 44 ± 1% to 51 ± 1% (P<0.01, N=5) which was greater (P<0.05) than the HCT rise following LTC_5. The latter results raise the possibility that reduced permeability to LPS in EFAD rats may be, in part, a result of preferential LTC_5 production which is less potent than LTC_4. (Supported by NIH GM 27673)

33 **INHIBITION OF ENDOTOXIN (LPS) INDUCED EICOSANOID SYNTHESIS AND PROCOAGULANT ACTIVITY BY PERITONEAL MACROPHAGES (MØ) OF RATS FED A LINSEED OIL ENRICHED DIET.** **J. N. Moore*, J.A. Cook, M.M. Henry*, P.V. Halushka, and W.C. Wise. College of Veterinary Medicine, University of Georgia, Athens, GA* and Medical University of South Carolina, Charleston, SC.**

LPS stimulates MØ to synthesize vasoactive mediators involved in the pathogenesis of circulatory shock. The eicosanoids arise from the metabolism of arachidonic acid in the membrane phospholipids. Alpha linolenic acid, a component of linseed oil, is metabolized to eicosapentaenoic acid, which may replace arachidonic acid in the phospholipids. Thus, ingestion of linseed oil may alter the generation of eicosanoids. MØ exposed *in vitro* to LPS express a procoagulant activity (PCA) which accelerates the recalcification time of plasma and may be important in LPS-induced coagulopathies. In this study, we compared LPS induced eicosanoid synthesis and expression of PCA by MØ from rats (n=5-6) fed a control diet and rats fed a diet enriched with linseed oil. Synthesis of immunoreactive (i) thromboxane B2 (iTXB2) and 6-ketoPGF1α (i6

-keto) and expression of PCA in response to 5 ug/ml LPS were compared at 6 hours:

Group:	iTXB2 ng/ml	i6-Keto ng/ml	PCA (%Tissue Factor)
Control	0.08 ±0.02	0.13 ±0.05	0.02 ±0.02
Linseed	0.29 ±0.11	0.16 ±0.05	0 ±0.0
Control + LPS	2.03 ±0.22	2.37 ±0.35	21.96 ±6.14
Linseed + LPS	0.79 ±0.11*	0.79 ±0.07*	0.81 ±0.05*
Control + A23187	15.67+1.41	15.29 ±0.81	Not Done
Linseed + A23187	14.36±1.19	13.34 ±1.02	Not Done

The data indicate that LPS-induced synthesis of eicosanoids and expression of PCA are reduced (*P<0.05) by incorporation of linseed oil in the diet, whereas the synthesis of eicosanoids stimulated by A23187 is not. The results suggest that linseed oil treatment has a selective effect on MØ responsiveness to LPS (NIH GM-27673).

34 PLASMA METHYLPREDNISOLONE LEVELS AND SURVIVAL IN RAT ENDOTOXIC SHOCK
E.Neugebauer, A.Dietrich*, J.Schirren*, W.Barthlen*, W.Lorenz; Institute of Theoretical Surgery and Surgical Clinic, University of Marburg, D-3550 Marburg, FRG

A variety of experimental septic/endotoxic shock studies demonstrated a significant protection against death by early treatment with methylprednisolone (MP). The effect is dose dependent: single bolus doses of MP < 50 and > 200 mg/kg b.w. were shown to be less effective in a rat endotoxic shock model. To estimate the minimum plasma levels and pharmacokinetics necessary for maximum protection, a randomized controlled study (4 groups, n=20 each) with a standardized rat endotoxic shock model (LD 70-100) was performed. Groups I and II (controls) received Endotoxin i.p. or 30 mg MP/kg b.w. i.v., respectively. In groups III and IV 30 and 50 mg MP/kg b.w. were administered intravenously together with the i.p. endotoxin. The plasma levels and pharmacokinetics of MP (HPLC-technique) were followed in 10 randomly selected animals from groups II-IV by collecting blood retroorbitally 9 times during the observation period of 96 h. – The survival rate in group I was only 30% (6/20) whereas 95% (19/20) of the animals in the high dose MP group (IV) survived. The maximum plasma levels determined at 5-30 min were always > 10 µg/ml (range 12-23). In contrast, only 70% (14/20) of the animals in group III survived. Maximum plasma levels never exceeded 10 µg/ml (range 1.2-9.4). All animals in group II survived with the same range of plasma levels as group III. No sign. differences were observed in the MP pharmacokinetics between all groups. Conclusion: A minimum plasma level of 10 µg MP/ml must be reached to get full protection which is also important for human studies and therapeutic drug monitoring attempts.

35 INHIBITION OF THE ENDOTOXIN-INDUCED HEMOCONCENTRATION IN CONSCIOUS RATS WITH THE PEPTIDOLEUKOTRIENE RECEPTOR ANTAGONIST SK&F 104353.
J.F. Newton*, M. Jugus*, R.D. Eckardt* and E.F. Smith III. Smith Kline & French Labs., King of Prussia, PA.

Endotoxemia is associated with plasma increases in a number of humoral factors, including vasopressin, thromboxane and leukotrienes (LT), which may mediate the pathophysiologic responses. Our previous studies demonstrated that S. enteritidis endotoxin-induced (30 mg/kg i.v.; LPS) hemoconcentration was attenuated with the peptidoleukotriene receptor antagonist SK&F 104353. The purpose of this study was to investigate the mechanism of the LPS-induced hemoconcentration. Injection of LTD_4 (51 nmole/kg, i.v.) increased the hematocrit in conscious male Sprague-Dawley rats by 5 vol%. Administration of SK&F 104353 (2 mg/kg, i.v. + 10 mg/kg/hr, i.v. infusion) completely inhibited this LTD_4 response. Injection of LPS increased the hematocrit from 40 ± 1 vol% to 55 ± 2 vol%. Pretreatment with SK&F 104353 attenuated the hemoconcentration to 46 ± 1 vol% ($p < 0.01$). Determination of plasma drug concentrations indicated that inhibition of the hemoconcentration by SK&F 104353 was concentration-dependent between 0.3 - 30 µg/ml (IC_{30} = 0.5 µg/ml). The stereoisomer, SK&F 104373, only weakly effected the hemoconcentration (IC_{30} = 50 µg/ml). BW 755C, a 5-lipoxygenase inhibitor, attenuated the hemoconcentration, whereas indomethacin, heparin, the V_1 AVP receptor antagonist $[d(CH_2)_5Tyr(Me)]AVP$, or daltroban were all without affect on the LPS-induced hemoconcentration. These results indicate that the LPS-induced hemoconcentration is mediated by peptidoleukotrienes, and that this response is stereoselectively inhibited in a concentration-dependent fashion with a peptidoleukotriene receptor antagonist.

36 SITES OF T CELL ACTIVATION INHIBITION BY A TRAUMA PEPTIDE
N. Ozkan* and D. Hoyt* (Spon: S.R. Shackford). University of California, San Diego Department of Surgery H-890A San Diego, CA 92103

Immunosuppressive activity of a trauma induced low molecular weight peptide (SAP) has previously been described. Immunologic activity of this peptide has been shown to be mediated by interference in the mobilization and utilization of calcium and calmodulin. The purpose of this study was to assess the activity of SAP on two calcium dependent T cell activation enzymes (cAMP phosphodiesterase and phospholipase C). Addition of peptide to in vitro assays measuring hydrolysis of cAMP or formation of inositol trisphosphate (IP3) resulted in marked inhibition in both systems.

I. Inhibition of cAMP Hydrolsis

Sample	% Inhibition cAMP hydrolysis
20 nmol SAP	23 %
30 nmol SAP	34 %
50 nmol SAP	61 %

II. Inhibition of Inositol Turnover

Time	% Inhibition IP3 Formation
5 min	94 %
10 min	44 %
15 min	61 %

To assess late effects of SAP on the activation cascade, early activation events were 'by-passed' utilizing a phorbol ester and a calcium ionophore to directly activate protein kinase C. The blastogenic response of SAP exposed PBLs at concentrations $\geq$70 nmol remained suppressive. From these data it appears that the trauma peptide can exert its effects both early in the T cell activation cascade, and at site(s) distal to these early events.

37 METABOLISM AND E. COLI ENDOTOXIN-INDUCED PRODUCTION OF CYSTEINYL LEUKOTRIENES IN DOGS. C. Pfeifer*, G. Bottoms, Purdue Univ. SVM, W. Lafayette, IN 47907.

Leukotriene (LT) metabolism was studied following an IV infusion of [14,15-^{3}H]-LTC_4 in anesth. dogs. Radioactivity (RA) was monitored in plasma, bile and urine for 3 hrs. LT metabolites (metab) were determined by HPLC and counting of collected 1 min fractions. Results revealed that 34.0% and 15.0% of the injected RA was recovered in bile and urine respectively within 3 hrs. Two identified metab in bile after 30 min were LTD_4 (30-53%) and LTE_4 (9-30%) which gradually decreased in amount. Three unidentified polar metab with retention times of 0.18, 0.27 and 0.36 that of [^{3}H]-LTC_4 (0.18LT, 0.27LT, 0.36LT) were found in bile and increased in conc. during 3 hrs. Primary metab in urine were LTE_4, 0.17LT and 0.35LT (30,43 and 25% after 30 min). No N-acetyl-LTE_4 was found in either bile or urine. In a second study, [^{3}H]-LTC_4 metabolism during E. coli endotoxin-induced shock (055:B5, 1.0 mg/ml, IV bolus) did not show a change in the types of metab, but total RA recovered in bile (20.4%) was decreased greatly after 3 hrs. In a third study, endogenous production of LTs was measured in bile in response to the E. coli infusion by HPLC, two mobile phases and a subsequent LT RIA. Peak bile levels of LTD_4 rose from 64 pg/ml (control) to an average of 6158 pg/ml and LTE_4 rose from 221 pg/ml to 2063 pg/ml 30 to 90 min after infused endotoxin (LPS). Collectively these results indicate that LTC_4 metabolism to LTD_4 and LTE_4 in the dog is similar to that in man, pig and monkey but dissimilar to that in rat. These results provide the first evidence of cysteinyl LT production following E. coli LPS infusion in an animal model that metabolizes LTs similiarly to man. (DOD, DAM 17-85-C-51-5100).

38 THE EFFECTS OF THYROID HORMONE ADMINISTRATION ON CARDIAC FUNCTION IN BURN SHOCK.
C.Price*, J.White*, J.Horton UT Southwestern Medical Center, Dallas, TX 75235-9031

Burn shock produces a defect in cardiac contraction and relaxation despite adequate fluid resuscitation. These defects are similar to those observed in the hypothyroid state. Since both free and bound thyroid hormone are decreased in experimental and clinical burns, we evaluated the cardiac effects of T-3 administration in combination with adequate fluid therapy in burn injury. Adult guinea pigs were subjected to a 40% TBSA, 3rd degree scald burn (Walker model), and then divided into Group 2 (lactated Ringer's (LR), 4 ml/kg/% burn for 24 hrs) and Group 3 (LR as above + T-3 0.025 ug/kg IV bolus with 0.34 ug/kg IV infusion over 24 hrs) with sham burns as Group 1. In vitro studies at 24 hours (Langendorf, coronary perfused heart preparation) showed that burn induced cardiac contractile

and relaxation deficits persisted with T-3 treatment. These data indicate little beneficial cardiac effects of this dose of T-3 in burn shock.

	Group 1 (N=15)	Group 2 (N=16)	Group 3 (N=9)
LVP (mmHg)	86.9±2.5	63.5±2.4*	61.3±4.5*
+dP/dt max (mmHg sec^{-1})	1374±48	1158±51*	1224±112
Time to max + dP/dt (msec)	56±1.9	48.6±1.1*	48.4±2.1*
-dP/dt max (mmHg sec^{-1})	1209±40	932±38*	891±84*
Time to max - dP/dt (msec)	70.8±2.1	61.8±1.6*	58.6±3.7*
Time to peak pressure (msec)	110.9±2.5	100.9±2.9*	95.2±3.9*

*Different from controls $p<.05$ (Neuman Keuls multiple comparisons)

39 MONOCYTE/MACROPHAGE ACTIVATION WITH CYTOKINE RELEASE AFTER POLYTRAUMA AND SEPSIS IN THE BABOON. H. Redl, G. Schlag, E. Paul, J. Davies*, Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria, * Roodeplaat Research Laboratories, Pretoria, South Africa.

As monocytes/macrophages act as key elements in the response to sepsis, we studied their pattern of activation by both cytokine and neopterin plasma analysis during sepsis and after polytrauma. Neopterin is a GTP derived metabolic product of monocytes/macrophages, which is released upon stimulation by gamma-interferon or endotoxin.

METHODS: Eight baboons were subject to hypovolemic-traumatic shock (HT) - or continuous live E. coli infusion (10^{10}CFU-animals) for 8 hours. Plasma was sampled and analyzed for neopterin, TNF, IL-1 and gamma-interferon by immunoassay.

RESULTS: Despite the severe trauma during HT shock, we neither found increased neopterin levels (baseline - BL = 0.08 ± 0.02 / end = 0.06 ± 0.02 nmol/µmol creatinine) nor increased cytokine concentrations, whereas the infusion of E. coli lead to a hyperdynamic septic state with an elevation of neopterin (BL - 0.4, 8 hours E.coli - 0.12 nmol/µmol creatinine), TNF (BL - 0.250, 8 hours - 0.500 ng/ml), gamma-IFN (BL - Ø, 8 hours - 4 U/ml), and IL-1 (BL - Ø, 8 hours - 200 pg/ml).

These results demonstrate that detectable monocyte/macrophage activation and cytokine release in baboons is associated with septic events, but not with polytrauma. Early organ damage may be related to ischemia/reperfusion and granulocyte action, while late organ failure could be due to monocyte/macrophage activation.

40 **HISTAMINE RELEASE IN SEPTIC SHOCK: CAUSED BY DRUG-INDUCED INHIBITION OF HISTAMINE METABOLISM?** **J. Sattler*, H. Sitter*, W. Woyke*, W. Dietz*, E. Neugebauer and W. Lorenz. Center of Operative Medicine I, Philipps-University, D-3550 Marburg, FRG.**

In our clinical trial septic shock patients showed elevated plasma histamine, ranging from normal to extremely high. This could be due to histamine release or drug-induced modulation of histamine breakdown via diamine oxidase (DAO). Therefore, we investigated 3 questions: Did these patients receive DAO-blockers? How were DAO-blockers distributed in the septic patients and the control group (with limb injuries)? Was there a correlation between number of blockers and plasma histamine levels? -- The patients (20 septic, 20 controls) received their drugs from a pool of 54. The water-soluble drugs were tested in vitro for their ability to inhibit human DAO. Statistical analyses were performed using rank tests and correlation coefficients. -- The septic patients received significantly more drugs (median 11; range 0-17) than the controls (1; 0-8) ($p<0.001$). 12 of the 54 drugs were potent DAO-blockers from important therapeutic groups (e.g. pancuronium, verapamil, imipenem). DAO-blockers were administered more in the septic patients (3; 0-4) than in controls (1; 0-2) ($p<0.001$). However, correlation analyses revealed no association between the number of DAO-blockers and plasma histamine levels. -- These results raise further questions: 1) Does an influence of DAO-blockade on plasma histamine levels in septic shock exist? 2) Can clinical side effects be caused by just 1 DAO-blocker? The results of our study on hemorrhagic shock demonstrated such an influence of DAO-blockade on plasma histamine. Either septic shock patients respond differently or the amount of DAO-blockade (not the number of blockers) is important.

41 EARLY ENDOTOXIN TOLERANCE IS ASSOCIATED WITH DIMINISHED TNF AND IL-1 PRODUCTION BY MONONUCLEAR CELLS. G. Wakabayashi*, B.D. Clark*, J.G. Cannon*, J.A. Gelfand*, C.A. Dinarello*, and J.F. Burke. Mass. Gen. Hosp. and New Engl. Med. Ctr., Boston, MA

We compared the production of TNF and IL-1 by isolated peripheral blood mononuclear cells (PBMCs) in vitro in response to endotoxin (LPS) with the febrile response of rabbits after serial endotoxin injections in vivo. PBMCs isolated from rabbits just prior to the first (day 0), second (day 1), and third (Day 7) LPS injection (50 ug, IV), were incubated for 24 hours with LPS (5 ng/ml). Total TNF levels (supernatant + cell lysates) were measured by the L929 bioassay. Total IL-1 levels were measured by the RIA for rabbit IL-1 developed in our laboratory. Rectal temperature after LPS injection showed a biphasic increase on day 0 (peak Δ BT; 1.225 ± 0.193°C, mean ± SEM), hyporesponsiveness on day 1 (no biphasic pattern, peak Δ BT; 0.575 ± 0.144), and hyper-responsiveness on day 7 (more intense biphasic pattern, peak Δ BT; 2.067 ± 0.433). TNF and IL-1 production in response to LPS was significantly reduced on day 1 [TNF (ng/ml); 1.7 ± 1.0 vs 7.4 ± 1.0 (day 0), p=0.003, IL-1 (ng/ml); 0.49 ± 0.2 vs 1.46 ± 0.3 (day 0), p=0.04]. On day 7, IL-1 production in response to LPS was increased (2.38 ± 0.1, p=0.04, vs day 0). A significant positive correlation was observed between peak Δ BT in vivo and IL-1 production in vitro after stimulation with LPS (r=0.687, p=0.04). In conclusion, these data show that prior exposure to endotoxin results in an inhibition of endotoxin-induced TNF and IL-1 production which may be one component of endotoxin tolerance.

42 **ALTERATIONS IN PLASMA LEVELS AND COMPLEXING OF GC (VITAMIN D-BINDING PROTEIN) IN RATS WITH ENDOTOXIC SHOCK.** **G.H. Watt*, S.A. Ashton*, J.A. Cook, W.C. Wise, P.V. Halushka and R.M. Galbraith*.** Medical University of South Carolina, Charleston, South Carolina 29425.

Septic shock is known to involve increased metabolism of arachidonic acid and generation of certain eicosanoids. Recently, a new extracellular pool of unsaturated fatty acids, including arachidonic acid, has been found in relation to Group specific component (Gc), a vitamin D-binding plasma protein which sequesters monomeric G-actin. Since complexed Gc with G-actin displaces fatty acids, possible alterations in plasma levels of Gc and extent of complexing were sought in serial samples obtained from rats with shock induced by *Salmonella enteritidis* endotoxin (12.5-15 mg kg^{-1}). Gc levels exhibited bimodal alterations, with a significant reduction one hour after administration of endotoxin, followed by a progressive elevation to 160% of starting concentrations at 6 days in animals that survived ($p<0.05$). In contrast to sham-injected animals, in which the percentage of Gc complexed remained <5%, statistically significant increases in complexing were observed in all endotoxemic rats from two hours onwards ($p<0.01$). Levels in survivors peaked at 30 ± 5% at eight hours and then decreased to normal (2 ± 1%) by 6 days (n=7), whereas in non-survivors complexed Gc continued to rise until time of death (66-80%) at 6-12 hours (n=4). Correlation of these results with glucose, transaminases, and immunoreactive TxB_2 and 6-keto-$PGF_{1\alpha}$ indicated that decreased absolute levels of Gc represent a consistent early change in endotoxic shock, and that the percentage of Gc complexed is an accurate prognostic indicator of shock severity. (Supported in part by NIH GM 27673 and DK 33082).

43 SOMATOSTATIN (SRIH) LEVELS ARE ALTERED DURING ENDOTOXICOSIS IN CONSCIOUS RATS. M.R. Yelich, B.A. Drolet* and D.M. Umporowicz*. Loyola Univ. Med. Center, Dept. of Physiology, Stritch School of Medicine, Maywood, IL 60153.

Glucoregulatory hormones such as insulin (IRI) and glucagon (IRG) significantly influence endotoxin-induced glucose dyshomeostasis. Since SRIH physiologically inhibits IRI and IRG secretion, alterations in SRIH levels may affect glucose dyshomeostasis during endotoxicosis. This study determined plasma levels of somatostatin-like immunoreactivity (SLI) in endotoxic rats. Arterial and venous catheters were placed in fed, male, Sprague/Dawley rats under anesthesia. 18-24 hrs later, conscious rats received iv 0.9% saline (S) or S. enteritidis endotoxin (E, 16.7 mg/kg). Levels of SLI, glucose (PG) and lactate (PL) were then measured in arterial plasma. SLI levels at various times after E injection are shown below as mean ± SE(n) pg/ml; p-value compares S vs E:

Time:	0	1hr	2hrs	3hrs	4hrs	5hrs
S	52 ± 14(7)	55 ± 16(7)	61 ± 16(7)	60 ± 17(7)	59 ±16(7)	58 ± 19(7)
E	43 ± 4(6)	341 ± 61(6)	230 ± 48(6)	146 ± 30(5)	123 ±35(5)	95 ± 48(3)
p	≥0.50	≤0.01	≤0.01	≤0.05	≥0.10	≥0.50

PG levels (mg/dl) increased from 109 ± 6(5) at time 0 to 296 ± 24(6) at 1hr, and then decreased to 32 ± 11(3) at 5 hrs after E. PL levels (mM) increased from 0.7 ± .06(5) at time 0 to 7.58 ± 3.1(3) at 5 hrs after E. Thus, E-induced changes in SLI levels were evident, as well as glucose dyshomeostasis. Since E-induced alterations in SLI levels paralleled those for PG levels, the results suggest that SRIH may play an important role in modulating the glucose dyshomeostasis of endotoxicosis by regulating insulin and glucagon secretion. (Support: NIH DK36044 and HL31163)

44 HYPERGLYCEMIA IN SUCKLING RAT ENDOTOXIC SHOCK. WP Zeller, M Goto, CE Menendez*, and RM Hurley*, Loyola Univ. Stritch Sch. of Medicine, Maywood, IL 60153.

In order to better understand the hyperglycemia of endotoxic shock in the immature rat, we evaluated the effect of adrenalectomy on endotoxic glucoregulation. Adrenalectomies were performed at least 3 days prior to the experiment. 10 day old rats were grouped as follows: Gr1 intact adrenal (saline 0.2cc IP), Gr2 adrenalectomy, Gr3 intact adrenal (S.enteritidis, LPS, 0.1 mg/kg IP, 24 hr lethality 90%) Gr4 adrenalectomy + LPS. Glucose PG mg/dl, insulin PI uU/ml, and lactate PL mM/L were serially tested after a 4 hour fast. (X±SEM *p<0.01)

Results:	Hrs.	Gr1(n>10)	Gr2 (n=4)	Gr3 (n=11)	Gr4 (n=11)
PG	0	94±2	105±5	-	-
	1	100±2	98±12	101±3	95±8
	2	88±2	90±17	112±4	66±9*
PI	0	27±2	27±9	-	-
	1	18±2	37±13	17±2	26±4
	2	17±2	20±1	17±2	40±7*
PL	0	1.3±.06	1.4±.10	-	-
	1	1.4±.04	1.1±.07	1.4±.03	1.03±.09
	2	1.4±.04	1.3±1.0	2.0±.08	2.0±.04

Endotoxic adrenalectomized animals were not able to mount a significant hyperglycemic response and hypoglycemia occurred rapidly. One can speculate the lack of hyperglycemia and the profound hypoglycemia in endotoxic adrenalectomized rats is related to the imbalance in insulin vs counterregulatory hormone response. (HLBI 31163)

45 **SENSITIVITY OF PORCINE RENAL, PULMONARY, AND SYSTEMIC VASCULATURE TO LEUKOTRIENE (LT) D_4: EFFECTS OF A LTD_4 RECEPTOR ANTAGONIST.** J. Zellner*, H. Reines, J. Cook, W. Wise, M. Reinhard*, P. Halushka, E. Smith. Medical University of South Carolina, Charleston, SC 29425 and Smith, Kline & French Laboratories, Swedeland, Pennsylvania 19479.

Vascular bed reactivity to exogenous LTD_4 and blockade of these responses by a selective LTD_4 receptor antagonist SKF 104353 (SKF) was studied. Yorkshire pigs (N=5; 30.4±5.6 kg) were anesthetized with isoflurane, and monitored for cardiac output (CO), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), right ventricular ejection fraction (RVEF), mean arterial pressure (MAP), renal artery blood flow (RABF), and systemic vascular resistance (SVR). LTD_4 (0.03, 0.1, .3, 1, 3 and 10.0 µg/kg) was given I.V. The MPAP, MAP, and RABF were recorded at baseline and for 20 min after LTD_4 injection. SKF was infused (3 mg/kg/hr) and the LTD_4 dose-response studies were repeated. LTD_4 induced changes in the MPAP, PCWP, MAP, and RABF. SKF only attenuated LTD_4 induced changes in the MPAP and RABF.

	LTD_4 * (ug/kg)			LTD_4 * (ug/kg) + SKF		
	0.03	3.0	10.0	0.03	3.0	10.0
%Δ RABF	-10.4±3.0†	-76.2±5.2†	-83±6.9†	-4.4±2.4	-33±7.1	-67±4.5
%Δ MPAP	-0.1±1.7†	123±24.2†	115±10.2†	7.0±3.1	-3.6±5.	36±8.6

*measurement at 40 sec after infusion of LTD_4; X± SEM; †p<0.05 LTD_4 vs. LTD_4 + SKF

The CO, RVEF, and CVP were not significantly changed by either LTD_4 or SKF at 1, 10, or 20 min. The LTD_4 induced changes in MAP, SVR, and PCWP were not blocked by SKF. In summary: 1) Porcine renal, pulmonary and systemic circulations are highly sensitive to LTD_4 and 2) SKF diminishes LTD_4 induced changes in RABF and MPAP but not MAP. The results suggest that subsets of LTD_4 receptors may exist in various vascular beds. (Supported by NIH GM 27673).

46 EFFECT OF HEPARIN, HIRUDIN, ANTITHROMBIN III (AT III), AND ANTITHROMBIN III-HEPARIN COMPLEX (ATC) ON ENDOTOXIN INDUCED DIC IN RATS. S. Bahrami, H. Redl and G. Schlag, R. Maschler*. Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria; * Plantorgan, Bad Zwischenahn, FRG.
Gram-negative septicemia is often associated with disseminated intravascular coagulopathy (DIC). The main anticoagulant function of heparin is to enhance the inactivation of serine proteinases in the coagulation cascade by AT III, which is consumed during activation. Compared to heparin, the hirudin effect is independent of AT III. Hirudin is not inactivated by the heparin neutralizing platelet factor IV released during shock. In this study we attempted to evaluate the prophylactic effect of infusion of an antithrombin-III-heparin-complex in endotoxemia induced in rats to 1) reduce the mortality (LD_{70}) and 2) ameliorate DIC and other physiological abnormalities. To study the individual contribution of each complex component we added groups treated with AT-III or heparin only. Furthermore we compared the effectiveness of prophylactic therapy with ATC to hirudin therapy. 50 animals were randomly divided into five groups of ten in each. Group CO - endotoxin (LPS) alone. Group HE - heparin 460 U/kg 1 hour pre-LPS. Group AT treated with AT III 400 U/kg 1 hour pre LPS. Group AC received a single dose of ATC containing about 80 U/kg AT-III and heparin 460 U/kg 1 hour pre LPS. Group HD - LPS + hirudin 4800 ATE/ kg bolus followed by 450 ATE/kg/h continuously up to 24 hours. Blood samples were taken for analysis of parameters related to DIC. Mortality at 48 hrs: CO = 70 % HE = 50 % AT = 50 % AC = 40 % HD = 75 %.
This study confirms the protective effect of combined AT-III and heparin against DIC during endotoxemia. (Hirudin was provided by Plantorgan.)

47 EFFECTS OF ALCOHOL INTAKE ON TOLERANCE TO LOW BLOOD PRESSURE FOLLOWING HEMORRHAGE. G. Bottoms, J. Fessler, M. Johnson, R. Coatney*, and B. Voorhees*. Purdue Univ., School of Veterinary Medicine, W. Lafayette, IN 47907.
The specific aim of this research was to test the hypothesis that intoxication with alcohol (given via stomach tube) resulted in poor tolerance to hemorrhage (40% of estimated blood volume). Four groups of six swine per group were used (control, intoxicated,hemorrhage and intoxicated-hemorrhage). The animal's tolerance to hemorrhage was evaluated on the basis of blood pressure (BP), cardiac output (CO), respiratory rate (RR), blood flow to different parts of the body (ml/100 g tissue), changes in blood chemicals and survival for 4 hrs after hemorrhage. The results revealed that blood alcohol concentrations near 0.1% greatly reduced tolerance to hemorrhage. Intoxicated animals subjected to hemorrhage were unable to maintain an adequate CO, BP, or RR to sustain life. Pigs tolerated higher blood alcohol concentrations, up to 0.35%, when not exposed to hemorrhage. Also, unintoxicated pigs were able to compensate for severe hemorrhage of 40% of the estimated blood volume. The numbers of pigs in each group that survived for 5 hours were as follows: control, 6; intoxicated, 6; hemorrhage, 4; and intoxicated-hemorrhage, 1. In conclusion the body's ability to compensate and recover from hemorrhage was greatly reduced during intoxication. It is logical to assume that the ability to overcome numerous other stressors may also be reduced during intoxication. (Supported by NIH grant R01 AA06851-01A1).

48 EFFECTS OF AN ENKEFALINASE INHIBITOR IN INTESTINAL SHOCK.
E. Haglind, J. Svanvik. Dept. of Surgery I, University of Göteborg, Sahlgren´s Hospital, S-413 45 Göteborg, Sweden.
Endogenous opioid peptides are suggested to be involved in the circulatory derangement in shock . Opiate antagonists, such as naloxon, have been reported to improve circulation and survival in endotoxin and hemorrhagic shock. Using a model of intestinal ischemia shock in the rat we found that administration of naloxon increased blood pressure but not survival. In this study in the same shock model the effects on blood pressure of an enkefalinase inhibitor (acetorphan=A) are reported. METHODS: 54 Wistar rats were used. Shock was induced in 4 groups by intestinal vascular obstruction (120 cm water for 60 min); 3 groups served as controls. A 0,3 mg (=0,06 ml) /100g bw was given iv every 20 min in one shock and one control group.The solute (SO) and saline (S) were given in the same manner and volumes .

Naloxone (N) was given as infusion (0,4 mg/100 g bw/h) during the entire 140 min-experiment. Blood pressure and hematocrit were determined. At 120 min naloxon (0,2 mg/100 g bw) was inj. iv to all but the naloxon-group. RESULTS: The shock group recieving A had significantly lower blood pressure than the other shock groups. Within the control groups blood pressue did not differ.The response to naloxone was significantly larger in the shock groups recieving Acetorphan and saline than in the corresponding control groups. The hematocrit was significantly higher in shock animals receiving A or S compared to the corresponding control group. CONCLUSIONS: Administration of an enkefalinase inhibitor results in decresed blood pressure in intestinal shock in the rat. This indicates that endogenous enkefalin may contribute to the circulatory derangement in intestinal shock.

49 ROLE OF ANGIOTENSIN IN NALOXONE AND IBUPROFEN THERAPY FOR CANINE ENDOTOXIN SHOCK
H. F. Janssen, J. A. Homan, C. D. Williams, P. A. Doris, J. B. Lombardini. Texas Tech Health Sciences Center, Lubbock, Texas 79430

The current study was undertaken to test the hypothesis that cardiovascular performance during endotoxic shock could be improved by blocking angiotensin-induced vasoconstriction and increasing cardiac performance with naloxone or ibuprofen therapy. Adult mongrel dogs of either sex were anthesitized with pentabarbatol sodium. The groups included: 1)saline control, 2)endotoxin only, 3)endotoxin plus captopril, 4)endotoxen plus naloxone, 5)endotoxin plus captopril plus naloxone, 6)endotoxin plus ibuprofen 7)endotoxin plus captrpril plus ibuprofen. Captopril was given as a bolus and continuous infusion starting 15 minutes prior to endotoxin, naloxone was given as a bolus and infusion starting 15 minutes prior to endotoxin and ibuprofen was given as a single bolus with endotoxin. The injection of endotoxin produced a depression in mean arterial pressure (MAP) similar to that previously reported. The additional administration of captopril to the endotoxin treated animals produced a further reduction in MAP. The administration of ibuprofen or ibuprofen plus captopril produced a significant increase in MAP reaching values similar to pre-endotoxin values. Naloxone produced a slight improvement in MAP while naloxone plus captopril resulted in a slight improvement in blood pressure initially followed by a decrease in MAP.
Supported by NIH Grant GM-35186

50 EFFECT OF ATP AND/OR INOSITOL ON GLUCOSE RELEASE BY THE LIVER IN RABBITS WITH HEMORRHAGIC SHOCK.
M. Jellinek, M. Shapiro, R. Abdulla, B. Vellareal-Loor, J. Standeven, and A. Baue. St. Louis University, St. Louis, MO 63110

During hemorrhagic shock hormonal responses, mediated by the action of phospholipase C on phosphatidylinositol bisphosphate (PIP_2), are expected to diminish membrane inositides. Since their recovery is energy and inositol dependent exogenous ATP and inositol were used as post-shock treatment. Glucose release by the liver in response to angiotensin II (A II) was used to assess a PIP_2 mediated response. Rabbits (28) were anesthetized and ventilated through a tracheostomy. Cannulas were inserted in the right carotid artery for blood withdrawal, the left jugular vein to just above the suprahepatic veins for continuous sampling by an automated blood glucose analyzer, the right femoral artery for blood pressure monitoring, and the left jugular vein for injecting A II (1.0 µg/Kg). While the animals' glucose levels were recorded continuously, a preshock (baseline) A II response was obtained. The animals were bled to 40mm Hg (90 min.), after which all blood was returned. Then treatments listed below (7 rabbits per group) lasted for one hour, after which another response to A II was recorded. Following shock and treatment with saline only, the ability of A II to mobilize glucose from the liver was 26.9+4.4% of baseline. The response was increased to 50.6+5.4% of baseline ($p<.01$) by treatment with 27 µmoles /Kg of ATP-$MgCl_2$ or to 63.7+7.1% of baseline ($p<.001$) with 27 µmoles/Kg of inositol. Addition of both ATP-$MgCl_2$ and inositol (27 µmoles/Kg each) restored the response to 72.3+6.6% of baseline ($p<.001$). This suggests that after shock the A II effect on glucose release declines and its recovery is inositol and energy dependent.

51 DOPAMINE AND MUSCLE TISSUE OXYGENATION. G. W. Lee*, P. J. Papadakos, E. Y. Cheng* and N. Lund*. Departments of Anesthesiology and Surgery, University of Rochester School of Medicine, Rochester, NY 14642 and Medical College of Wisconsin, Milwaukee, WI53226

In, e.g., hypovolemic shock pulmonary artery catheters are used to assess fluid and vasoactive drug requirements. In spite of the availability of these tools, mortality in critically ill patients has not improved significantly. One explanation is that centrally derived parameters give very little information about the state of the individual organs. The effects of dopamine on skeletal muscle are of interest since blood flow to muscle can be varied widely, thus affecting the whole body. We therefore studied the effects of dopamine infusion (2.5, 5 or 10 mcg/kg/min given in randomized order) on muscle pO_2 in normoxemic rats. Tissue pO_2 data were collected before, during and between infusions with the 8-channel MDO oxygen electrode (Kessler & Lübbers). Blood was drawn for arterial blood gas analyses and hematocrits. Mean arterial blood pressure was monitored, and in order to maintain normovolemia the volume of the blood samples was transfused from a donor rat. Dopamine in low doses (2.5 and 5 mcg/kg/min) decreased tissue oxygenation. Dopamine at 10 mcg/kg/min, however, increased tissue pO_2. Other parameters did not change significantly. The decrease in tissue pO_2 at low dose infusions of dopamine may be due to a redistribution of blood flow to other vascular beds. The increased tissue pO_2 seen at 10 mcg/kg/min is probably due to the alpha-receptor effect of dopamine at this dose level with less preferential flow to, e.g., the kidneys, thus increasing perfusion pressure through the muscle bed.

Kessler M, Lübbers DW. Aufbau und Anwendungsmöglichkeit verschiedener PO_2-elektroden. Pflügers Arch ges Physiol 1966;291:R82.

52 ENTERAL ALLOPURINOL IN INTESTINAL ISCHEMIA. S.Megison*, J.Horton, H.Chao*, P.Walker* UT Southwestern Medical Center, Dallas, TX 75235-9031

Studies demonstrating protective effects of allopurinol in intestinal ischemia have been carried out using IV allopurinol (presently unavailable for human use) or enteral allopurinol at supra-normal doses and, therefore, have questionable clinical relevance. We evaluated the protective effects of clinically used doses of enteral allopurinol in rats with intestinal ischemia. Ninety-nine male Sprague-Dawley rats (250-300 gms) received enteral allopurinol (5-30 mg/kg) or water daily for one week and were subjected to superior mesenteric artery occlusion for 20, 30, or 45 min.

MORTALITY RATES

Ischemic	Treatment Groups				
Groups	Water	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day	30 mg/kg/day
20 min	50% (N=10)	*0% (N=10)	*0% (N=10)	*0% (N=10)	----
30 min	71% (N=7)	----	----	75% (N=8)	90% (N=10)
45 min	90% (N=10)	----	93% (n=14)	----	80% (N=10)

*p=0.016 compared to water fed controls (Fischer's test)

We conclude that: 1) prolonged intestinal ischemia causes lethal damage during the hypoperfusion phase that can not be prevented by allopurinol pretreatment even at supra-normal doses, and that 2) allopurinol at recommended enteral doses (5-10 mg/kg/day) can reduce mortality from reperfusion injury when the phase of hypoperfusion is not, in itself, lethal. Allopurinol is effective in reducing reperfusion injury in the currently available enteral form in dose ranges that should not cause prohibitive side effects.

53 THE EFFECTS OF PROTEASE INHIBITOR FUT-175 ON PHOSPHOLIPASE A2, COMPLEMENTS, PROSTAGLANDINS AND PREKALLIKREIN DURING ENDOTOXIN SHOCK. Y. Okuda, H. Ogata, Y. Midorikawa. Department of Anaesthsiology, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Tochigi, 321-02, Japan

This experiment was performed to investigate protease inhibitor FUT-175 (Nafamostat mesilate, FUTHANE) on the blood pressure, phospholipase A2, complement (3), CH50, thromboxane B2, 6-keto-PGF1α and prekallikrein during endotoxin shock using 19 dogs. LPS was injected at a dose of 3 mg/kg in 11 dogs. 8 dogs were injected with 2 mg/kg of FUT-175 before administration of LPS, and then infused continuosly with 50 µg/kg/min. of FUT-175 during experiment. FUT-175 revealed about a 14-26 % increase of the blood pressure and suppressed totally activations

of phospholipase A2 as well as a 20 % of prekallikrein but not in serum TXB2, 6-keto-PGF1α , C3 and CH50 compared with the LPS alone group. It was considered for these reasons of suppression of phospholipase A2 and increase of the blood pressure that FUT-175 inhibited indirectly prekallikrein system.

54 EFFECTS OF ADRENERGIC AGENTS ON OXYGEN UTILIZATION DURING HYPERDYNAMIC SEPSIS A. Paschall*, L. Hoban*, J. Hermiller*, D. Reusch*, J. Carcillo*,(Spon: J. R. Fletcher). Naval Medical Research Institute, Bethesda, Md. 20814-5055 and Children's Hospital, Washington, DC 20010.

The purpose of this study was to determine the effects of alpha and beta adrenergic agents on O_2 utilization. The day after instrumentation, ten Yucatan minipigs (18-29kg) were given 2-4x10^{10} E. coli via a peritoneal catheter. Twenty-four hours later all animals received an infusion of dobutamine at 20 mcg/kg/min, and one hour later a phenylephrine infusion of 30 mcg/kg/min was added. Measured O_2 saturations and cardiovascular parameters were recorded at baseline and at 60 minutes during each infusion. Data expressed as mean$\pm$1 std; a-p<.05 vs. base and b- p<.05 vs. beta.

	BASE	BETA	BETA + ALPHA
CI (ml/kg/min)	185 ± 38	288 ± 70[a]	194 ± 27[b]
SVRI (dynes-sec-cm^{-5}/kg)	42 ± 13	25 ± 6[a]	43 ± 9[b]
DO_2 ($ml/O_2/kg$)	23 ± 5	35 ± 10[a]	24 ± 4
VO_2 ($ml/O_2/kg$)	6.8 ± 0.9	7.8 ± 0.8[a]	8.5 ± 1.4[a,b]
EXT (VO_2/DO_2)	0.3 ± .06	0.23± 0.5[a]	0.36± 0.5[a,b]

Beta stimulation increased O_2 consumption (VO_2) as cardiac index (CI) and O_2 delivery (DO_2) increased. A fall in O_2 extraction (EXT) was also seen. Alpha stimulation caused a divergence from flow dependance as VO_2 increased despite a fall in CI and DO_2. This occurred as a result of improved extraction. Addition of an alpha agent may therefore increase systemic vascular resistance (SVRI) and maintain an elevated VO_2 despite causing a decrease in CI and DO_2.

55 ALTERATIONS OF PMNL-FUNCTION BY PENTOBARBITAL VERSUS CHLORAL HYDRATE IN A HEMORRHAGIC SHOCK MODEL IN THE RAT. M. Rose*, V. Bühren, O. Gonschorek*, S. Rose*, O. Trentz. Dept. of Trauma Surgery, Univ. of Saarland, D-6650 Homburg/Saar, FRG.

Although barbital is reported to show a suppressive tendency, data on the influence of anesthetic agents on the microbicidal activity of polymorphonuclear neutrophil leukocytes (PMNL) are inconsistant. Luminol-enhanced chemiluminescence (LECL) was used to investigate alterations of PMNL-function by monoanesthesia with pentobarbital (PB, 60 mg/kg bw) versus chloral hydrate (CH, 360 mg/100g bw) in a hemorrhagic shock model in the rat. Two groups of male Lewis rats (315 ± 25 g bw) received either PB or CH anesthesia, followed by a two-step blood withdrawal of 2.5 ml/100 g bw. Measurement of LECL with BaseLine and Shock plasma was accompanied by monitoring of hemodynamics, Hb and gas exchange.

	MABP mmHg		Hb mg/dl		pH		BE mmol/l		LECL cpmx10^3/10^3cells	
	PB	CH	PB	CH	PB	CH	PB	CH	PB	CH
BaseLine	132	86*	15.5	13.6#	7.40	7.39	+3.8	+2.8*	56.7	61.5
Shock	40	29*	9.8	9.5	7.32	7.24*	-6.9	-9.2*	33.4	36.7

Mann-Whitney-U-Test between PB and CH: * $p \leq 0.05$; * $p \leq 0.01$; # $p \leq 0.001$

Although induction of hemorrhagic shock in rats anesthetized using pentobarbital versus chloral hydrate led to highly significant differences in hemodynamics and gas exchange, suppression of LECL response was independent on anesthetic substance, indicating no specific suppression by barbital.

56 KAPPA OPIOID RECEPTOR AGONIST ADMINISTRATION INTO BRAIN CARDIOREGULATORY NUCLEI WORSENS OUTCOME AFTER HEMORRHAGIC SHOCK IN RATS. S.B. Samuels, N.S. Yeston and T.K. McIntosh. Dept. of Surgery, Univ. of Conn. Health Ctr., Farmington, CT 06032

The central cardiovascular response to shock is thought to be regulated in part by hindbrain nuclei, including nucleus ambiguus (NA). Since endogenous opiate receptors are localized throughout these areas, activation of endogenous opioid systems there may be expected to affect post-shock cardiovascular compensation and mortality. The present study examined the effects of central administration of the kappa-receptor agonist, U-50488H (Upjohn) on cardiovascular function and mortality in fixed-volume hemorrhage in rats. Sprague-Dawley rats (n=10) underwent unilateral femoral artery and vein cannulation and stereotaxic placement of an indwelling 26-gauge guide cannula into the NA under pentobarbital anesthesia. The following day, 15 min. prior to the the induction of hemorrhage, awake animals received a microinjection of either U-50488H (100 nM in 50 nl, n=5) or saline (equal volume, n=5) into the NA. A fixed blood volume (7.5cc/300 gm b.w.,or 40%) was then withdrawn. MAP in all animals fell from 113 ± 3 mmHg to a minimum of 60 ± 4 and showed a compensatory rise at the end of hemorrhage. Although control animals maintained this compensation for a prolonged period, MAP in U-50488H-treated rats fell soon after post-hemorrhage compensation (x=80 ± 16 mmHg vs. 112 ± 4 mmHg for controls at 8 min. post-shock). Animals treated with U-50488H showed a marked trend towards shorter survival (x=17 min.) compared with controls (x=384 min., p=ns). These results suggest that kappa opioid receptor activation in NA exerts a deleterious effect in hemorrhagic shock.

57 PENTAFRACTION REDUCES THE LUNG DAMAGE OF ENDOTOXEMIA. L.Traber, J.Toole*, J.Coffey*, and D.Traber. Univ. of Tx Med. Br. & Shriners Burns Inst. Galveston, Tx 77550.

The response to endotoxin (LPS) in the ovine lung lymph preparation is characterized by an elevation in pulmonary microvascular permeability which is manifest some 3 hrs after the onset of the response. These changes are documented by a rise in lung lymph flow (LQ) with a concomitant fall in cardiac output (CI) and rise in the lymph to plasma oncotic pressure ratio (L/P). We tested a new high molecular weight (mw 350,000) starch compound, Pentafraction (PF), to determine it's effects on LQ. Sheep were prepared (n=15) seven days prior to study and divided into two groups. Group ZE received 15 ml/kg of a solution containing 6% PF. Group PE received 15 ml/kg of ovine plasma. Two hrs post treatment the sheep were given a bolus of LPS (1 mcg/kg) and studied for 24 hr. PE group showed a typical response to LPS. At 3 hrs there was an elevation in LQ with rich in oncotically active agents. These changes were associated with a lowering of (L/P) and and Increase the plasma to lymph oncotic pressure gradient (P/L-GR). Addition of high molecular weight starch maintains the oncotic pressure gradient during this time and reduces the rise in LQ. These changes are even more important when the CI was higher with compound PF administration during the time of lung injury and thus there was an increased surface area perfusion in the treated animals. NIH #HL34552 Dupont #607-87-TR.

Time	plus lps	LQ	Ponc	L/P	P/L-GR	CI	PAP
CONT.	PE	13±3	18±1	0.61±.08	8±1	6.7±0.5	23±1
	ZE	7±1	21±1	0.61±.03	9±1	6.9±0.5	22±1
3 hr	PE	33±7*	17±1	0.74±.04	5±1	4.8±0.3	27±1
	ZE	13±2	18±1	0.64±.03	7±1	5.9±0.5	27±2

58 CALCITONIN GENE-RELATED PEPTIDE (CGRP) LEVELS IN PLASMA ARE ELEVATED DURING HEMORRHAGIC SHOCK AND RESPONSES REVERSED BY EARLY BLOOD REPLACEMENT OR DEXAMETHASONE TREATMENT. X. Wang*, C.D. Han*, M. Qi*, M.C. Chen* and R.R. Fiscus* (Spon: S.B.Jones). Dept. Pathophysiology, Beijing Medical University, Beijing, People's Republic of China 100083 and Dept. Physiology, Loyola Univ. Medical Center, Maywood, IL 60153.

Previously we showed that plasma levels of CGRP and neuropeptide Y are elevated during pathogenesis of endotoxic shock and that dexamethasone (Dex.) blocks the CGRP response. In this study we investigated effects of hemorrhagic (hem.) shock on plasma CGRP levels and effects of dex. and blood replacement. Male Wistar rats (250-300g) were anesthetized by urethane and cannula implanted in carotid artery for bleeding or mean arterial pressure (MAP) measurements. Another cannula was implanted in external jugular vein for blood replacement or Dex. administration. Hem. shock was made by bleeding into blood reservoir maintaining MAP at 35 mm Hg. Blood samples were taken and plasma CGRP levels measured by a specific RIA after purification over C_{18} Sep-Pac columns. We found that hem. shock lead to significant elevations in plasma CGRP levels at 30, 60, 90 and 120 min (23.8±1.9, 22.3±1.3, 20.3±2.4 and 49.5±5.8 pg/ml vs. control = 11.1±1.1 pg/ml,

P<0.001-0.002), and CGRP levels at 120 min were significantly higher than at other time points (P<0.005). Blood replacement after 30 min, but not 120 min, of shock returned plasma CGRP levels and MAP back to normal. When Dex. (5 mg/kg) was also given with blood replacement at 120 min, plasma CGRP levels were reduced to 23.9±2.8 (vs. 39.2±5.6 pg/ml with blood replacement alone). These data indicate that plasma CGRP levels are elevated in hemorrhagic shock and this may contribute to the pathology of late decompensatory phase. Blood replacement, if early, or Dex. can reverse this CGRP response.

59 OXYGEN RADICALS DISTURB ENDOTHELIAL CELL MORPHOLOGY AND INTRACELLULAR FREE CALCIUM DYNAMICS. D. Franceschi*, D. Graham*, J. Galat*, M. Sarasua*, (Spon: Robert S. Rhodes). Case Western Reserve Univ., Cleveland, OH 44106 and Univ. of Mississippi, Jackson, MISS, 39216

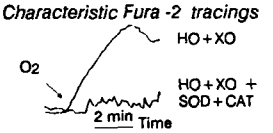
Disturbances in cellular Ca^{2+} homeostasis have been implicated in tissue injury resulting from exposure to oxygen radicals. To characterize these changes in endothelial cells, we have studied the dynamics of intracellular free Ca^{2+} ($[Ca^{2+}]_i$) in bovine aortic endothelial cells after exposure to superoxide utilizing the fluorescent probe Fura-2 AM. Monolayers of endothelial cells were exposed to superoxide radicals generated with hypoxanthine and xanthine oxidase (HX+XO). This system generated up to 20.7 uM of O_2^- as determined by the ferricytochrome C assay. Continuous measurement of Fura-2 fluorescence intensity reveals a significant and substantial rise in intracellular calcium which occurs within seconds from exposure to the free radicals.

$[Ca^{2+}]_i$ (nM) *IN ENDOTHELIAL CELLS - EFFECT OF O_2^- PRODUCTION*

TIME(sec)	CONTROL	HX+XO	SOD+CATALASE
0	125 ± 34	135 ±55	131 ± 58
60	115 ± 51	510 ± 98 *	236 ± 57 **
300	134 ± 44	914 ± 134 *	218 ± 63 **

Mean±SD *p<0.05 vs control **p<0.05 vs HX+XO (Student's t test)

Characteristic Fura -2 tracings



The rise in intracellular Ca^{2+} produced by superoxide is sustained over the experimental period and this effect is blocked by superoxide dismutase (SOD) and catalase. Morphometric digital analysis of the cells demonstrates a significant loss of adherence accompanied by a change in perimeter (smaller; $p < 0.03$) and form (stellate to round) after exposure to the free radicals suggesting cytoskeletal injury. Likewise, protection against these shape changes was provided by SOD + catalase. A similar alteration in cellular morphology is observed when endothelial cells are exposed to high doses of the calcium ionophores ionomycin (10uM) and A23187 (100nM) indicating that the sustained elevation of intracellular calcium caused by superoxides may contribute to the observed changes in shape and size. In summary, oxygen free radicals cause a significant rise in intracellular calcium in endothelial cells shortly after exposure. This rise in calcium may contribute to the morphologic alterations observed.

60 INFLUENCE OF A LINSEED OIL ENRICHED RATION ON THE RESPONSE TO ENDOTOXIN IN HORSES. **M.M. Henry* and J.N. Moore. College of Veterinary Medicine, University of Georgia, Athens, GA.**

Some of the most devasting clinical problems associated with endotoxemia in horses are due to alterations in the microvasculature, including vasoconstriction and thrombus formation. Many of these effects of endotoxin are due to alterations in the phospholipids in cellular membranes resulting in the generation of vasoactive eicosanoids from arachidonic acid and the expression of monocyte procoagulant activity (PCA). Because certain inflammatory processes are dependent on the fatty acid composition of the cellular membrane, dietary manipulations which replace arachidonic acid with omega-3 fatty acids may modify the inflammatory response. We investigated the effect of supplemental alpha linolenic acid, an omega-3 fatty acid, on the response to endotoxin in horses. Linseed oil was the source of alpha linolenic acid. One group of horses (n=6) was fed a control (C) pelleted ration (0% linseed oil) and another group of horses (n=6) was fed an 8% linseed oil (LO) pelleted ration. After 8 weeks of feeding, endotoxin induced generation of monocyte PCA and immunoreactive thromboxane B2 (iTxB2) were significantly reduced (50% and 80%, respectively) in vitro, in the LO group. Subsequently, the horses were infused with 0.03 ug/kg *E. coli* 055:B5 endotoxin over 30 minutes, and iTxB2, 6-ketoPGF1a (i6-keto), and whole blood recalcification times (WBRT) were compared at baseline, 1, 3, and 12 hours. [* p<0.05 between times; ψ p<0.05 between groups]

	Baseline		1 hour		3 hours		12 hours	
	C	LO	C	LO	C	LO	C	LO
iTxB2 (pg/ml)	151 ±65	238 ±59	1550 ±77*	1802 ±234*	476 ±91	604 ±122	138 ±67	186 ±115
i6-keto (pg/ml)	137±12	219±18ψ	521 ±77*	516 ±71*	318±63	416±76	227 ±77	208±16
WBRT (sec)	683±33	868±31ψ	-	-	596±33	711±29ψ	496 ±30*	605±35ψ*

Although LO reduces the in vitro generation of endotoxin-induced monocyte PCA and iTxB2, and prolongs WBRT, it does not not alter the in vivo generation of eicosanoids in response to endotoxin.

61 EFFECT OF ENDOTHELIAL CELL CONFLUENCE ON CELLULAR GLUTATHIONE LEVELS AND RESISTANCE TO OXIDATIVE INJURY. R. Holman*, T. Kavanagh*, R. Maier. U. Washington, Seattle, 98195

Oxidant-induced injury to microvascular endothelial cells(EC) may be central to the development of vascular leak and subsequent multiple organ failure. In tumor cells, cell-cell contact and increased intracellular reduced glutathione(GSH) contribute to enhanced resistance to oxidants. In this study, the potential roles of these processes in EC resistance to oxidants are evaluated. In rabbit pulmonary EC *in vitro*, loss of cell energy levels as a marker of cytotoxicity were determined by HPLC-measured cellular ATP levels. GSH was assessed by flow cytometry using monochlorobimane. Injury was induced by a 2hr. exposure to glucose oxidase(GOX) generated H_2O_2 in parallel plates at selected time points (i.e. increasing confluence).

GOX	ATP(nm/10^6 EC)				N=4-10±SEM
(mU/ml)	2-3	4-5	6-7	8-9 x10^6 EC/plate	
0	13.63±.62	12.81±.36	11.69±.29	10.30±.55	*p<.05
50	4.44±1.1*	9.37±.40*	9.05±.77	8.35±.91	compared to
100	1.48±.58*	4.15±.45*	6.34±1.1*	6.77±1.6*	control

Cell density dependent cytoprotection was confirmed by injuring identical cell numbers at different cell densities. A two-fold increase in cells/plate (an indicator of cell density) was associated with a 12.1% decrease in basal GSH. As with ATP, oxidant induced decreases in GSH were abrogated by increased cell density. Conclusions: Increasing EC density and/or cell contact correlate with a marked cytoprotective effect for oxidant-induced EC injury. Unlike tumor cell lines, enhanced EC resistance did not correlate with increased basal glutathione levels.

62 MACROPHAGES (MØs) INDUCE NEUTROPHIL (PMN) EMIGRATION BY A NON-CD18 MECHANISM OF ADHERENCE. W. Mileski*, R. Winn, J. Harlan, C. Rice, Univ of Washington, Seattle Wa. 98104

(PMN's) play a central role in the genesis of the multiple organ failure syndrome resulting from shock and sepsis. PMN adherence to endothelium is necessary prior to PMN emigration and is thought to be largely mediated by the PMN membrane protein CD18 which can be blocked by the monoclonal antibody (MAb) 60.3. One exception is the lung, an organ with a large resident Mø population, where PMN emigration in response to Streptococcus pneumoniae (S. pneu) has been demonstrated to occur by a non-CD18 mechanism. We asked the question: Are Møs capable of inducing PMN emigration by a non-CD18 mechanism? PMN emigration in the peritoneum of rabbits was examined under 3 conditions: 1) normal peritoneum, 2) Mø-enriched peritoneum, and 3) Mø-enriched then depleted by washing. Mø-enrichment was achieved by instilling peptone protease in the peritoneum 72 hrs prior to experiments and resulted in a 20-fold increase in Møs. Each group was sub-divided into control and MAb 60.3 treated (2 mg/kg) subgroups prior to peritoneal instillation of 10^{10} bacteria (S.pneu or E.coli). Peritoneal lavage was performed 4 hrs after bacterial injection. Lavage PMN counts (x 10^{-6}/ml±SD) and % inhibition by MAb 60.3 are given below.

	S. pneu (n=30)			E. coli (n=20)	
	Normal	MØ-enriched	Washed	Normal	MØ-enriched
Control	1.67±.35	2.75±.58	2.37±.18	0.96±.36	2.33±.4
MAb 60.3	0.16±.03	1.74±.4	0.30±.12	0.13±.08	0.26±.05
Inhibition	89.2%	36.5%	87.7%	88.7%	88.4%

MAb 60.3 blocked >85% of PMN emigration in both E. coli groups and in the normal and washed S. pneu groups while PMN emigration in the Mø enriched S. pneu group was only 36.5% inhibited (p<.05 t-test). These results suggest that Mø products released by S.pneu, but not by E. coli, can induce PMN emigration by a non-CD18 mechanism of adherence.

63 DOES ENDOTOXIN PLAY A MAJOR ROLE IN THE SUPPRESSION OF MACROPHAGE (MØ) ANTIGEN PRESENTATION (AP) FOLLOWING HEMORRHAGE? A. Ayala*, M.M. Perrin* and I.H. Chaudry. Dept. of Surgery, Michigan State University, East Lansing, MI 48824-1315.

Studies indicate that hemorrhage in the absence of major trauma can suppress the host's immunoresponsiveness. Endotoxemia, due to bacterial translocation from the gut during hypotension, has been postulated to play a role in this suppression. The aim of this study was to determine whether or not the process of MØ AP, an important component of both cell-mediated and humoral immunity, differentially affects endotoxin-tolerant C3H/HeJ, as compared to endotoxin-intolerant C3H/HeN mice, following hemorrhage. To study this, mice were bled to and maintained at a mean BP of 35 mmHg for 60 min and then resuscitated with their own blood and adequate

fluids. Mice were sacrificed 24 h later to obtain both splenic (sMØ) and peritoneal MØ (pMØ), which were assessed for their capacity to present antigen (conalbumin) to a sensitized cloned T-cell line (D10.G4.1). Hemorrhaged C3H/HeJ mice exhibited a significant ($P<0.05$) decrease in AP which was similar for both sMØ (-79.0+5.2%) and pMØ (-81.0+17.7%), and is comparable to that observed with C3H/HeN. The capacity of these MØ from C3H/HeJ mice to produce IL-1, as well as express membrane bound IL-1 on their cell surface showed no significant differences. However, a marked decrease was observed in the % of Ia antigen positive MØ in both C3H/HeJ and C3H/HeN mice, indicating that reduced AP following hemorrhage is related to the inability of these cells to express Ia. These results suggest that endotoxin may not play a major role in the depression of MØ AP following hemorrhage or in the enhanced susceptibility to sepsis observed following severe hypotension (Supported by NIH GM 37127).

64 A CLINICALLY RELEVANT MODEL OF HEMORRHAGIC SHOCK AND RESUSCITATION IN THE RAT. I.H. Chaudry, K.A. Blasko*, P.A. Wagner*, P. Wang*, D. Hunter-Simon*, J.G. Hauptman. Department of Surgery, Michigan State University, East Lansing, MI 48824-1315.

Most hemorrhagic shock models require heparinization of the animals prior to the induction of hemorrhage. In the clinical situation, however, accident victims are not heparinized prior to incurring the injury and blood loss. In order to more closely approximate this situation, male S-D rats weighing 309±5 g (mean±SE) were lightly anesthetized and a 5cm midline laparotomy performed (i.e., trauma induced). The incision was then closed in layers and a carotid artery, jugular vein and a femoral artery were cannulated using PE 50 tubing. The portion of the PE 50 tubing inserted into the vessel was narrowed to decrease the internal diameter by approximately 50%. The unrestrained rats were then allowed to awaken and rapidly bled to and maintained at a mean BP of 40 mmHg until 40% of the shed blood volume was returned in the form of Ringer's lactate (RL). The rats were then resuscitated with 2 X the volume of maximum bleed out with RL, the catheters removed and the incisions closed. Food and water was allowed ad lib and survival was measured over a period of 5 days. The mortality rate in this model despite volume resuscitation was 58% (19/33) and at autopsy, the liver and kidney showed marked necrosis. The surviving rats, 42% (14/33), demonstrated a significantly decreased blood flow to various organs and a body weight loss of 40±7g at 3-5 days post resuscitation. This model of trauma (i.e., laparotomy), hemorrhage and resuscitation in the conscious, non-heparinized and unrestrained rat may be useful in evaluating therapeutic interventions for potential clinical applications (Supported by NIH GM 39519).

65 EFFECTS OF SINGLE PERIOD AND INTERMITTENT AORTIC BLOCKADE AFTER HEMORRHAGIC SHOCK IN THE RAT. O. Gonschorek*, V. Bühren, M. Rose*, I. Marzi* and O. Trentz. Dept. of Trauma Surgery, Univ. of Saarland, D-6650 Homburg Saar, FRG.

Aortic cross clamping is known to be a potential life-saving procedure in otherwise fatal hemorrhage. To prevent or diminish massive reperfusion injury after declamping, a treatment schedule with intermittent opening of aortic occlusion has been recommended. In our hemorrhagic shock model intermittent aortic blockade was compared to continuous clamping of varying times. Male Lewis rats received pentobarbital anesthesia (60 mg/kg bw) followed by a two step blood withdrawal of 2.5 ml/100g bw. Resuscitation after 30 minutes of hypovolemia consisted in subphrenic supraceliacal aortic clamping (gr.A-10'; gr.B-20'; gr.C-30'; gr.D-2 x 10' with 10' clamp free interval; sham-no clamping) and retransfusion of shed blood after clamp release.

	MAP' (mmHg)			pH			Survival
	BaseLine	Clamp	Reperf.	BaseLine	Clamp.	Reperf.	at 150' (%)
sham	132±11	38± 4	71±10	7.38±0.01	7.28±0.03	7.40±0.04	100
gr.A	134±10	71± 9*	77± 9	7.41±0.02	7.36±0.02*	7.34±0.03	100
gr.B	132± 7	62±13*	58±10	7.41±0.03	7.32±0.03	7.34±0.04	86
gr.C	134± 8	61±10*	33± 5*'	7.38±0.01	7.30±0.04	7.11±0.05*'	43
gr.D	134± 4	72±13*	37± 5*'	7.39±0.02	7.30±0.05	7.20±0.07*'	57

*,' - $p \leq 0.05$ (Two-tailed Mann-Whitney-U-test: * compared to sham, ' to B)

Significant deterioration of recorded values was observed during reperfusion if clamping time exceeded 20'. A schedule of intermittent occlusion showed aggravation of reperfusion injury compared to same duration of clamping without interval-opening.

66 MEASUREMENT OF RAPID PLASMA VOLUME EXPANSION AFTER INFUSION OF HYPERTONIC SALINE USING CHANGES IN PLASMA PROTEIN CONCENTRATION.
L Halvorsen*, KD Ashley*, RD Hands*, S Nakayama*, GJ Smith*, JW Holcroft, and GC Kramer. School of Medicine, University of California, Davis, CA 95616, and Letterman Army Institute of Research, San Francisco, CA 94129.

Hypertonic saline/dextran infusions cause rapid plasma volume expansion (PVE). In our previous studies, Evans blue measured plasma volume at 10 minutes post infusion was increased 3.4±0.3 ml for each ml of 7.5% NaCl/6% dextran 70 infused into hemorrhaged sheep (n=31). Direct measurement of this expansion by dye dilution is time consuming and can only be performed for a few time points. We hypothesized that the decrease in hemoglobin concentration, [Hb]; hematocrit, (Hct); or plasma protein concentration, [P], might be used as an index for volume expansion. Equations were derived which allowed calculation of % plasma volume expansion (%PVE) as a function of [Hb], Hct or [P] assuming no vascular-extravascular exchange, changes in RBC volume or differences in large vessel versus small vessel Hct. Retrospective analysis of 6 studies of sheep infused with both isotonic and hypertonic solution (n=75) demonstrated a higher correlation between %PVE estimated from changes in [P] and measured PVE (Evans Blue) than either [Hb] or Hct. The latter two parameters overestimated PVE by 125±35% (n=5) and 51±8% (n=75) respectively vs 13±16% (n=16) for [P] ($p<.05$). Explanations for this overestimation include changes in [Hb] and Hct secondary to erythrocyte shrinkage, large vs small vessel Hct, and splenic uptake of RBC's. While no parameter produces an ideal correlation, the formula: $\%PVE = ([P]_{initial} - [P]_{final}) / [P]_{final} \times 100$ could provide a useful means of monitoring rapid plasma volume expansion in both animals and man.

67 FILTRATION ASSISTED BLOOD EXCHANGE FOR THE EVALUATION OF BLOOD SUBSTITUTES.
JR Hess*, CE Wade, RM Winslow* (Spon: J O'Benar), Letterman Army Inst. of Research, Presidio of San Francisco, CA 94129

Modified hemoglobin solutions support life in the absence of red blood cells (RBCs). Understanding of the physiology and toxicity of such solutions has been retarded by the limited quantities of well characterized material. Exchange transfusion studies in large animals are a particular problem because of the volumes of material required, three blood volumes for 95% replacement of RBCs, and because of concomitant removal of albumin and clotting factors with conventional exchange techniques. An exchange technique was developed for continuous flow blood filtration with the CPS-10 Plasma Separator (Fenwal, Deerfield, IL) which removes all blood cells while returning 60% of the plasma. By filtering blood at 70 ml/min and replacing retained volume with 14 g/dl hemoglobin solution, 20 kg immature swine had 95% of RBCs removed while 20% of initial plasma was retained. Two liters of hemoglobin solution were used. This procedure was performed on eight anesthetized swine with no change in blood pressure during and one hour after exchange. Central venous pressure rose from 4 to 12 cm H_2O and cardiac output increased from 2.3 to 2.8 L/min. This exchange technique is efficient and allows evaluation of RBC substitutes.

68 CHARACTERIZATION OF A PORCINE MODEL OF INTRA-ABDOMINAL SEPSIS.
L. Hoban*, A. Pascal* L. Jones*, J. Nevola*, J. Carcillo*, (Spon. R. Fletcher) Naval Medical Research Institute, Bethesda, MD 20814-5055 and Children's Hospital, Washington, DC 20010

The purpose of this investigation was to develop an awake, reproducible porcine model of intra-abdominal sepsis. The day after invasive vascular lines were inserted, sixteen male Yucatan minature swine received $1\text{-}4X10^{10}$ E. coli/kg through an intraperitoneal catheter. Hemodynamic parameters were obtained prior to, hourly for six hours, and 24 hours post the administration of bacteria. Data are expressed as mean ± 1 std; *$P < 0.05$ vs. Baseline.

	BASELINE	3 HR	24 HR
Cardiac Index (ml/kg/min)	156±24	92±23*	208±25*
Mean Systemic Art. Pressure	93±5	72±11*	89±5
Mean Pulm. Art. Pressure	19±5	39±12*	26±3
Systemic Resis. Index(dynes-sec-cm^{-5}/kg)	46±7	61±15*	29±3*
Pulm. Resis.Index (dynes-sec-cm^{-5}/kg)	6±3	25±8*	26±5*

Serum measurements of creatine, SGOT, SGPT, and pathologic analysis of autopsy specimens revealed evidence of severe multi-organ dysfunction. Blood cultures were positive in 60% and mortality 4 days after sepsis was 56%. In conclusion, we have developed a simple, reproducible model of intra-abdominal sepsis in the unanesthetized awake swine that is characterized by: (1) hypodynamic state on day 1 with low cardiac output secondary to pulmonary hypertension; (2) hyperdynamic state on day 2 with low systemic resistance and high cardiac index. This system should serve as an excellent large-animal model for the study of septic shock.

69 ACUTE EFFECTS OF CORE-LPS (RE-595) INTRAVENOUS INFUSION ON SYSTEMIC HEMODYNAMICS IN THE CONSCIOUS RABBIT. G. JESMOK, P. HOLLAND*, AND J.R. KOPPLIN.* Cetus Corporation, Emeryville, CA 94608.

The acute systemic hemodynamic effects of endotoxin (LPS) administration vary depending on the dose, route, species, and state of the experimental animal preparation (conscious or anesthetized). High dose LPS infusion is associated with an acute decline in arterial blood pressure in the pentobarbital-anesthetized preparation. In these series of experiments, we examined the acute systemic hemodynamic effects of high dose LPS (Re-595, 300-350 ug/kg) in the conscious rabbit. The animals (2-3 kg, N=6) were surgically instrumented under Ketamine/Rompum anesthesia, to record: Mean Arterial Pressure (MAP), Cardiac Output (CO) by thermal dilution, and Systemic Vascular Resistance (SVR, MAP/CO). Hemodynamic measurements were performed in the conscious rabbit over five hours (beginning 2 to 3 hours following surgery). Intravenous LPS (Re-595) did not result in a decline in MAP. The acute response in the conscious rabbit was characterized by a 40% decline in CO (216± 9 ml/kg/min to 130 ± 15 ml/kg/min at 5 hours $p < 0.05$) with a 93% increase in SVR ($p < 0.05$). Heart rate and body temperature also increase significantly. The decline in CO following LPS challenge may be related to myocardial depression but is more likely related to a maldistribution of blood flow, with severe venous pooling and decreased venous return. The experiments further emphasize the dependence of the circulatory changes induced by LPS on the experimental model employed.

70 E. COLI ENDOTOXIN PRODUCES HYPERDYNAMIC HEMODYNAMICS IN THE RAT

Thomas D. Johnston*, William H. Hampton*, and Donald E. Fry
Case Western Reserve Univ., Cleveland, OH 44106

The discovery of endotoxin-induced mediators, including tumor necrosis factor and interleukin-1, has sparked renewed interest in the role of endotoxemia in sepsis. However, sepsis is associated with hyperdynamic hemodynamics while endotoxin shock has generally produced a hypodynamic picture. To examine the relevance of endotoxemia to septic shock, rats were anesthetized and cannulated. Baseline cardiac output (CO) and systemic vascular resistance (SVR) measurements were made. They then received one of four E. coli endotoxin infusions per 100 mg rat weight over 20 min.: 1) saline control, 2) 0.01 mg, 3) 0.10 mg, 4) 1.00 mg. After 60 min., CO and SVR were re-measured and effective hepatic blood flow (EHBF) was measured by galactose clearance.

RESULTS (±SEM), % change calculated as postinfusion vs. baseline

GROUP	% Change CO	% Change SVR	EHBF/CO ratio	
1 (N=8)	-4.5±5.4	-0.8±0.8	0.19±0.018	(*p<0.05 vs.)
2 (N=6)	25.5±11.3*	-20.2±5.6*	0.21±0.047	(control)
3 (N=7)	-31.7±11.1*	41.6±5.6*	0.17±0.019	
4 (N=7)	-19.7±16.4	49.6±29.6	0.13±0.017*	

These data indicate the characteristic septic hemodynamic profile followed low doses of endotoxin. Higher doses were associated with depressed CO and increased SVR. Reduced EHBF/CO at higher endotoxin doses indicate a greater reduction in hepatic blood flow than could be explained by decreasing cardiac output alone. Since septic hemodynamics can be produced by endotoxin infusion, models which focus on lower endotoxin doses may more closely model clinical septic shock.

71 PATTERN OF HEPATIC CELL NECROSIS IN A SHOCK/REPERFUSION MODEL IN THE RAT.
I. Marzi*, V. Bühren, F. Blessing*, S. Rose*, G. Harbauer*, and O. Trentz.
Departments of Trauma and Experimental Surgery, University of Saarland, 6650 Homburg/S., FRG.

The purpose of this study was to develop a method to assess liver cell damage in experimental hemorrhagic shock. Shock was induced in 30 Sprague Dawley rats by withdrawal of 2.5 ml/100 g BW over 30 min (MABP declined from 125.3 to 44.6 mmHg). Thereafter, aortic cross clamping was performed for 15 min and shed blood was retransfused upon declamping. 150 min following shock induction, the liver was perfused for 5 min with Krebs-Henseleit bicarbonate buffer containing trypan blue (200 µM) and subsequently processed for histological examination. Counterstaining with eosin allowed determination of trypan blue positive nuclei and semiquantitative evaluation of cell damage (Scoring system: 1: scattered staining = < 15 %; 2: < 50 %; 3: < 80 %; 4: > 80 % cell death). Unexpectedly, a pronounced midzonal necrosis was observed besides pericentral cell injury. Midzonal and pericentral necrosis (mean score 2.4; sham group 0), however, was a consistent pattern of cell death following hemorrhagic shock. This reliable and uncomplicated technique represents a useful tool to evaluate pathophysiology of liver cell damage as a consequence of ischemia/reperfusion injury in hemorrhagic shock.

72 CLOSED LOOP CONTROL OF PENTOBARBITAL ANESTHESIA IN BABOONS.
J. Newald, J. Davies*, G. Schlag. Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria, * Roodeplaat Research Laboratories, Pretoria, South Africa.

The effects of most anesthetics on myocardial contractility and on the autonomous nervous system demand tight control of the level of anesthesia and analgesia in spontaneously breathing baboons.

We used frequency spectrum analysis to monitor the burst suppression rate induced by pentobarbital sodium infusion at a rate of 0.2 to 8 mg/kg/hour. A special intracranial EEG electrode was implanted on the dura mater in the central frontal region, and an extracranial needle electrode was placed in the occipital region of the skull. EEG sampling periods were 2 seconds, end-expiratory CO_2 was collected every 10 seconds. FFT power spectra were calculated and the first moment of power in the range from 2..8 Hz was used as a parameter for judging the depth of anesthesia. This level was expressed as a score in the range of 0..1000, with higher scores indicating higher electrical activity. The delivery of pentobarbital sodium by a Braun Perfusor Secura was controlled by the microprocessor via an RS-232 interface. We used a simple PI algorithm for closed loop control starting from baseline anesthesia defined by a cardiac output of 120..150 ml/kg. The mean EEG score was 346 ± 74. Anesthesia was discontinued whenever endexpiratory CO_2 exceeded 55 torr. Satisfactory control even during hypovolemic polytraumatic shock was achieved in 31 animals. The mean duration of control was 6.9 ± 1.4 hours. Drug consumption was minimized: the mean supply of pentobarbital sodium was 3.2 ± 2.2 mg/kg/h. EEG-triggered anesthesia maintained a stable level of analgesia for several hours with no impairment of respiration or hemodynamics.

73 BACTERIAL TRANSLOCATION IN A BABOON MODEL OF HYPOVOLEMIC-TRAUMATIC SHOCK.
G. Schlag, H. Redl, K. Radmore*, J. Davies*. Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Vienna, Austria, * Roodeplaat Research Laboratories, Pretoria, S.A.

We were interested to see whether bacteremia occurs early after hypovolemic-traumatic shock in our baboon model.

MODEL: This model in EEG-controlled anesthetized baboons involves closed femur fracture, soft tissue injury and hypovolemia (40 mmHg) over 4 hours, as well as resuscitation over 2 hours (reinfusion shed blood + Ringer's solution 1:1).

MICROBIOLOGY: Tissue samples were taken under aseptic conditions and cut finely, placed in Enterobacteriaceae enrichment broth and spread on MacConkey plates. Further isolation of cultures and identification was done using Tryptone Soy Agar plates, oxidase test (Gen. Diagnostics), Enterotube (Roche) and Oxi/ferm tube (Roche). Blood was taken 1 + 1 with Roche blood culture medium.

RESULTS: In the ongoing experiments 4 of 4 shock animals revealed bacterial translocation with e.g. E. coli, Klebs. pneumoniae, Proteus mirab., Enterobact. cloacae and Pseudomonas in mesenteric lymph nodes, spleen, liver and blood cultures, while the small bowel was always sterile. In controls no positive cultures were found in the same organs.

CONCLUSION: Severe hypovolemic-traumatic shock with resuscitation in baboons similar to the human polytrauma situation immediately results in bacterial translocation of pathogenic germs in the large bowel. This is in accordance with macro- and micropathological results of lesions in the GIT at the end of these experiments.

74 HEMORRHAGIC SHOCK AND BACTEREMIA IN A NON-RESUSCITATED RAT MODEL. J. Spiers*, G. Voeller*, L. Trenthem*, and I. Fabian. Univ. Tenn., Dept. Surg., Memphis, TN

Hemorrhagic shock has been associated with both immunosuppression and bacterial translocation from the gastrointestinal tract; the significance and route of translocation are unresolved. Using a rat model in which 35% of the animal's estimated blood volume was shed, non-resuscitated rats had their peritoneum, portal blood and systemic blood cultured at one, twenty-four or forty-eight hours after hemorrhage:

		Positive Cultures in Post-Shock Period		
		1 Hour	24 Hours	48 Hours
Shocked	Peritoneal Cavity	5/5*	6/6	11/17*
	Portal Blood	2/5	3/6	4/17
	Systemic Blood	3/5	2/6	3/17
Controls	Peritoneal Cavity	0/3	0/3	0/4
	Portal Blood	0/3	0/3	0/4
	Systemic Blood	0/3	0/3	0/4

*$p<0.05$ using Fisher's Exact Test when compared to controls.

In all groups the peritoneal cavity was the most common site of bacterial growth. All organisms were normal rat enteric flora. All animals with positive portal or systemic cultures also had positive peritoneal cultures.

The data shows that hemorrhagic shock is associated with bacterial translocation from the gastrointestinal tract to the portal venous system, the system circulation and the peritoneal cavity. Translocation of intestinal bacteria to the portal and systemic circulations occurs when the peritoneal cavity has been colonized.

75 COMPARISON OF LOW VS. HIGH DOSE E. COLI INFUSION IN IMMATURE SWINE. K. Stewart, F. Straughn, L.B. Hinshaw. Okla. Medical Research Found. Oklahoma City, OK 73104.

We developed a model of gram (-) sepsis in fasted, spontaneously breathing, sodium pentobarbital sedated swine (4-7 weeks), of unselected gender. The animals received a 120 min infusion of live E. coli (ATCC #33985) at either low ($4-10 \times 10^7$ organisms/kg) or high dose ($5-10 \times 10^8$ organisms/kg). Data were collected during infusion (0-120 min), early post infusion (120-240 min) and late (240-360 min). Significant differences did not exist between the low and high dose groups at T=0. All changes in measured variables mentioned below are significant ($p < .05$) with respect to T=0. The low dose group (n=5) showed: early and late hypoxia with O_2 desaturation at 60 and 180 min, late hypocarbia, and early thrombocytopenia which persisted. The high dose group (n=5) had: hypotension during infusion with recovery after 180 min, late tachycardia, immediate hypoxia with O_2 desaturation, early leukopenia which was sustained, late thrombocytopenia and hemoconcentration, plus late hypoglycemia. When the two groups were compared (low dose vs. high dose), the high dose group had: lower pH (300 and 360 min), lower mean arterial pressure (90,120, and 180 min), higher hematocrit (360 min), increased heart rate (90-360 min), lower O_2 saturation (240 min), increased respiratory rate (60,90, and 120 min) and initially higher (120 min) then lower (360 min) platelet counts. The animals who received a higher bacterial load showed changes also described in patients with sepsis. Therapeutic intervention, in this model, will be made after lethal dose determination using a seven day survival protocol.

76 PHAGOCYTIC CELL AND RES FUNCTION IN RECURRENT ENDOTOXEMIA IN SHEEP. A. Seekamp*, G. Regel*, A. Owenger*, M. Weidner*, J.A. Sturm*, (Spon: H.J. Oestern). Unfallchirurgische Klinik, Klin. Biochemie, Medizinische Hochschule Hannover, West Germany.

The sepsis syndrome in severely traumatized patients is supposed to be due to a blockade of the phagocytic cell systems e.g. reticulo-endothelial system (RES) and polymorphonuclear leukocytes (PMNL) which cause an insufficient elimination of bacterial substances (e.g. endotoxin). In contrary we could find that in acute endotoxemia RES clearance is enhanced while the PMNL function shows signs of decompensation. In order to clarify whether our results were just a matter of the single dose endotoxemia, we have investigated RES and PMNL function in a sheep model with recurrent endotoxemia. Eight sheep were monitored over a 5 day period receiving endotoxin (ET) at a dose of 1µg/kg BW every 12 h. RES clearance was calculated by the half-life time of Tc99-phytate on each day. PMNL function was determined by measurering chemiluminescence (CL) of isolated PMNL and whole blood. The half-life time of Tc99-phytate decreased from 56 min. by endotoxin down to 44 min. ($p<0.01$) at the 2nd day and further to 42 min. ($p<0.002$) at the 3rd day. Till the end of study, values returned to baseline. Zymosan induced and luminol enhanced CL response indicated an acute cellular exhaustion after the first ET dose. Under subsequent ET administration a daily attenuation of the acute response was noted, parallel to a continuous decrease of C3b receptor concentration. Our results give evidence that also in recurrent endotoxemia the RES is characterized by a sufficient clearance, whereas the PMNL function remains decreased and is therefore probably responsible for the well known clinical posttraumatic septic complications.

77 ISCHEMIA-INDUCED CHANGES IN ENERGY PHOSPHATES AND NICOTINAMIDE NUCLEOTIDES IN LIVER AND INTESTINE A. Canada, W. Brooks*, R. Harrell*, K. Stein*, W.D. Watkins, and R. Bollinger* Duke U. Med. Ctr., Durham, NC.

The effect of ischemia on intracellular biochemicals has been widely studied, particularly in heart and liver. These have focused on high energy phosphates (HEP), their breakdown products, and intracellular energy charge. Less studied has been the effect of ischemia on nicotinamide adenine nucleotides (NAN) despite their role in intracellular oxidative processes, including the formation of ATP.

We have begun *in situ* studies in rats to explore the role of NAN and HEP in ischemic injury of the liver and intestine. Initially, we compared the effect of 30 min of total ischemia of the left liver lobe with that of SMA occlusion (intestine) on both HEP and NAN content.

In non-ischemic organs, we found a small difference in HEP between liver, 4.33 +/- 0.35 and intestine, 2.95 +/- 1.11 nmoles/wet weight (nMWW). However, we found a significant difference between the liver and intestine in NAD+, 0.48 +/- 0.35 and 0.12 +/- 0.02 nMWW. After 30 min of total ischemia, the liver HEP content decreased to 2.84 +/- 0.36 nMWW while none occurred in the intestine. The liver NAD+ content decreased to 0.14 while the intestine dropped to 0.08 +/- 0.02 nMWW. Ischemia produced a decrease in oxidized NAN in both the liver (from 0.67 +/- 0.06 to 0.34 +/- 0.09 nMWW) and intestine (0.17 +/- 0.02 to 0.10 +/- 0.02 nMWW). We hope these studies will lend insight into intracellular markers of reversible vs/ irreversibe tissue injury.

78 ULTRAFILTERABLE MAGNESIUM CONCENTRATIONS IN CRITICALLY ILL CHILDREN. B. Chernow, J. Roa*, L. Eguiguren*, G. G. Stanford*, L. Napolitano*, I. D. Todres*, D. L. Gargano*, M. Stoiko*, Departments of Anaesthesia and Pediatrics, Harvard Medical School/Massachusetts General Hospital, Boston, MA 02114

Total serum hypomagnesemia is a common metabolic abnormality in critically ill adults, observed in 50-70% of patients (Chest 1989; 95:391-397). Reports concerning magnesium (Mg) metabolism in critically ill children are lacking. Since there are no ion-selective electrodes for measuring serum ionized Mg, we have instituted studies of the Mg concentration in ultrafiltrates of serum. This latter measurement is an excellent correlate of ionized values of divalent ions. We, therefore, measured the serum ultrafilterable Mg concentration in 118 normal subjects (age range: 50-80 years). We also measured this variable on ICU admission blood samples from 23 critically ill children (age range: 2 months - 16 years). Mg determinations were

performed using sensitive and specific assays. Results: In our normals, the normal range for serum ultrafilterable Mg concentrations was 0.9-1.5 mEq/L (0.45-0.75 mmol/L). This variable increased slightly with increasing age ($y=1.0647x + 0.00306$; $r=0.411$, $p<0.01$). In the 23 critically ill children, 3 of 23 (13%) had ultrafilterable hypomagnesemia. This percentage of ultrafilterable hypomagnesemia is similar to what we previously found for ionized hypocalcemia in adults (12%) and children (17%). Conclusion: Hypomagnesemia is relatively common in critically ill children and should be considered in evaluating the critically ill child.

79 RELATIONSHIP BETWEEN RESTING ENERGY EXPENDITURE AND TOTAL ENERGY EXPENDITURE IN BURNED CHILDREN. M. I. Goran, E. J. Peters and R. R. Wolfe. Shriners Burns Institute, Galveston, TX 77550.

Existing knowledge of energy expenditure in burned patients is based on spot measurements of resting energy expenditure (REE) by indirect calorimetry, without considering its relationship to total energy expenditure (TEE). The doubly labeled water technique was used to measure TEE over 7 days in burned children. This novel technique involves calculation of TEE from simultaneous measurement of the turnover rates of the stable isotopes of water, $H_2{}^{18}O$ and ^2H_2O. The relationship between REE and TEE was examined in 6 burned children (aged 5-14), with severe burn injury, (56-80% of body surface area was 2^o burn, 31-68% of body surface area was 3^o burn) over 7 day periods commencing 20-39 days post-burn. REE was 1.15 ± 0.098 times the Harris-Benedict prediction of basal energy expenditure (BEE), and TEE was 1.61 ± 0.28 times BEE. REE contributed $75.4 \pm 9.9\%$ of TEE. The children remained weight stable on diets that provided, on average, 2.36 ± 0.19 times predicted basal caloric requirements. These data therefore suggest that the hypermetabolic response to burn injury has ended by 3-5 weeks post-burn. In addition, the rational for use of sustained hypercaloric feeding remains unclear, and further studies are required to understand the need for excessive provision of calories to maintain stable body weights in convalescent burned children.

80 FED AND FASTED STATES ALTER ENDOTOXIC SHOCK IN SUCKLING RATS. M Goto, WP Zeller, CE Menendez*, RM Hurley* Dept. Ped. Loyola Univ. Stritch Sch. Med., Maywood, IL 60153

Adult rats become more resistant to endotoxin(LPS) 12-24 hrs after food deprivation(DP). Newborn responses to LPS are different from adults. To evaluate effects of DP on newborn endotoxic shock, glucoregulation in 10 day old Sprague-Dawley rats was studied. Experiment 1: Rats received ip injection as follows: Gr1, 0.2 ml saline immediately after DP; Gr2, S. enteritidis LPS(0.1mg/kg) immediately after DP; Gr3, saline 24 hrs after DP: Gr4 LPS 24 hrs after DP. During DP, rats were kept in an incubator. Plasma glucose (PG) and lactate (PL) were determined. Glucose tolerance test (GTT); 1.2g/kg ip) was performed after saline or LPS injection at 4 hrs in Gr1 and Gr2 and at 6 hrs in Gr 3 and Gr4. Experiment 2: Rats were grouped as in Experiment 1. At 4 hrs in Gr1 and Gr2 and 6 hrs in Gr3 and Gr4, liver ex situ was perfused with Krebs Ringer bicarbonate(KRB) or KRB plus 5 mM/L of lactate to observe liver glucose production (LGP).

Results:

	PG(mg/dl)					LGP(mg/g) at 75 min.	
hrs.	0	2	4	6		KRB	KRB+lactate
Gr2	121±5	161±9	83±6	29±6	Gr2	0.2±0.1	3.0±0.3
Gr4	95±1	101±11	139±2	95±4	Gr4	0.3±0.3	8.4±1.1

LPS increased PL to 6.50±2.04 and 3.81±0.38 mM/L at 6 hrs in Gr2 and Gr4, respectively. DP decreased 24 hr mortality of endotoxic shock (90% in Gr2 vs 38% in Gr4,$p<0.001$) GTT reveal a diabetic pattern in Gr4. Conclusion: DP preserved liver gluconeogenesis in suckling rats with endotoxic shock and decreased glucose utilization. We speculate that blunting hypoglycemia by DP reduced mortality. (HLBI 31163)

81 PHORBOL 12-MYRISTATE 13-ACETATE (PMA) AUGMENTS LETHALITY AND GLUCOSE DYSHOMEOSTASIS IN ENDOTOXICOSIS. H. Inaba* and J.P. Filkins. Loyola University Medical Center. Maywood, IL 60153

To investigate the role of protein kinase C (PKC) activation in endotoxin (ETX) shock, we studied the effects of PMA, a potent PKC activator, on ETX-induced lethality and glucose dyshomeostasis in vivo. Fed, male Holtzman (Harlan) rats (300-400 g) were treated with incremented doses of ETX i.v. (S.enteritidis) and either the vehicle, dimethyl sulfoxide (DMSO), 110 mg/kg i.p. or PMA dissolved in DMSO, 0.5 mg/kg i.p. While PMA was non-lethal, it significantly increased ETX-induced lethality:

		ETX dose (mg/kg)				
Treatment	0 (Saline)*	1.0*	2.5*	5.0*	10.0*	20.0**
		number of deaths/number of animals tested (%)				
DMSO	0/10(0)	2/18(11)	3/17(18)	6/24(25)	9/16(56)	10/15(67)
PMA in DMSO	0/10(0)	10/18(56)	10/18(56)	20/24(83)	17/17(100)	16/16(100)
p value		<0.01§	<0.05§	<0.001§	0.024§§	0.035§§

* lethality at 24 hr after ETX; ** Lethality at 5 hr after ETX.
§ chi-square test; §§ Fisher's exact probability test.

Sequential determinations of plasma glucose and lactate under pentobarbital anesthesia revealed that PMA sensitized rats to the hyperglycemic and hypoglycemic responses to ETX (1 mg/kg). These results suggest that PKC activation may be involved in the pathogenesis of lethal endotoxicosis and associated glucose dyshomeostasis.
Supported by NIH grant HL31163.

82 MECHANISM FOR THE DEPRESSED LEVELS OF BLOOD KETONE BODIES DURING GRAM-NEGATIVE SEPSIS. S. Lanza-Jacoby, J. Lukish*, E. Rosato*, G. Braccia*, and A. Tabares*, Department of Surgery, Jefferson Medical College, Philadelphia, PA 19107.

To investigate why blood ketone bodies (KB) are depressed during sepsis, we studied the production and utilization of KB in fasted control (C), fasted E.coli-treated (EC), fed C and fed EC rats. The EC rats were injected with 8 x 10^7 live E.coli colonies/100 body weight. Fed rats were infused intragastrically with a nutritionally adequate diet for five days prior to inducing sepsis. Twenty-four hours after E.coli injection, ketogenesis was not altered in hepatocytes from fasted EC rats compared with their C. E.coli sepsis did not affect labeled palmitate oxidation ($^{14}CO_2$ and ^{14}C acid-soluble products) by isolated hepatocytes from fasted EC rats. Ketone production by hepatocytes from fed EC rats declined by 75% ($P \leq 0.01$). Oxidation of labeled palmitate was also reduced by 78% ($P \leq 0.01$) in hepatocytes from the fed EC rats. Utilization of KB, as measured by the incorporation of [3-^{14}C] B hydroxybutyrate (OHB) into CO_2, increased over 3-fold in the diaphragm (EC: 14.9 $\pm$ 2.6 nmol/g/hr; C: 3.9 $\pm$ 0.9, $P \leq 0.01$) from EC rats. Smaller, but significant increases were also noted in the heart (EC: 20.1 $\pm$ 0.4 nmol/g/hr; C: 17.9 $\pm$0.4, $P \leq 0.01$) and kidney (EC: 9.9 $\pm$ 0.2 nmol/g/hr; C: 8.0 $\pm$ 0.6, $P \leq 0.05$) of the EC rats compared with the C rats. In fed rats the incorporation of [3-^{14}C] OHB into CO_2 increased 5-fold in the heart (EC: 52.9 $\pm$ 2.6 nmol/g/hr; C: 10.5 $\pm$ 0.9, $P \leq 0.001$), 4-fold in the diaphragm (EC: 18.3 $\pm$ 4.5 nmol/g/hr; C: 1.3 $\pm$ 0.1, $P \leq 0.001$) and over 3-fold in the kidney (EC: 33.6 $\pm$ 1.2 nmol/g/hr; C: 8.7 $\pm$ 0.6, $P \leq 0.001$) from the EC rats. These results suggest that plasma ketones remain low during gram-negative sepsis because peripheral tissues use more KB and liver ketogenesis is not increased to compensate for the increased utilization. Supported by grant GM 3128-01A2 to SLJ from NIGMS.

83 THE ROLE OF INSULIN AND GLUCOSE OXIDATION IN MEDIATING THE PROTEIN CATABOLIC RESPONSE TO BURN INJURY AND SEPSIS. F. Jahoor, R. E. Shangraw, H. Miyoshi, D. N. Herndon, R. R. Wolfe. Shriners Burns Institute, Galveston, TX 77550.

We have investigated the responsiveness of protein kinetics to insulin and the role of glucose oxidation in mediating the protein catabolic response to burns and sepsis by assessing the response of leucine kinetics to a 5 hour hyperinsulinemic euglycemic clamp with and without simultaneous administration of dichloroacetate, DCA, (to further increase glucose oxidation via stimulation of pyruvate dehydrogenase activity) in 8 burned and 8 septic patients. Leucine flux and oxidation were measured by the primed-constant infusion of 1-^{13}C-leucine and used as indices of the absolute and net rates of protein breakdown. Basal leucine

flux (5.15 ± 0.24, 4.08 ± 0.22 and 2.78 ± 0.16 um/kg.min in burned, septic and controls) and leucine oxidation (1.6 ± 0.14, 1.25 ± 0.15, and 0.61 ± 0.07 um/kg.min in burned, septic and controls), was significantly elevated ($P<0.01$) in both groups of patients compared to controls indicating a stimulation in the total and net rates of protein breakdown. The hyperinsulinemic clamp elicited significant ($p<0.05$) and similar decreases in leucine flux and oxidation in both groups of patients which was comparable to the reduction induced in controls. The administration of DCA in patients during hyperinsulinemia elicited a significant increase ($p<0.05$) in the rate of glucose oxidation compared to the rate during the clamp alone yet there was no change in the response of leucine kinetics. We conclude that neither an impairment in the effectiveness of insulin to suppress protein breakdown nor a deficit in glucose oxidation is responsible for the protein catabolic response to burns and sepsis.

84 IN VIVO INSULIN RESPONSIVENESS OF INDIVIDUAL TISSUES IN SEPSIS. C.H. Lang, C. Dobrescu* and K. Meszaros*. Physiology, LSU Medical Center, New Orleans, LA 70112

Hypermetabolic sepsis produces whole body insulin resistance. The present study was performed to determine in vivo which tissues are responsible for the sepsis-induced decrease in insulin-stimulated glucose utilization. Vascular catheters were placed and sepsis produced by subcutaneous injections of E. coli. In vivo insulin action was assessed 20 h after the first injection of bacteria by combining the euglycemic hyperinsulinemic clamp and the tracer 2-deoxyglucose (dGlc) techniques. Insulin was infused at various rates in separate groups of septic and nonseptic rats for 3 h to produce steady-state insulin levels between 70-20,000 uU/ml. Tracer dGlc was injected at 140 min into the clamp for determination of the glucose metabolic rate (Rg) in selected tissues. The maximal response to insulin was decreased 30-40% in the gastrocnemius, and the red and white quadriceps. The former two muscles also showed a decrease in insulin sensitivity (i.e., increased ED_{50}). However, the insulin resistance was not evident in all muscles since insulin action in abdominal muscle, diaphragm and heart was not different between septic and nonseptic animals. Basal Rg of skin, spleen, ileum and lung from septic animals was higher than non-septic values and remained higher at each insulin concentration. The Rg of ileum and spleen was unresponsive to insulin in septic animals. This study indicates that the decreased Rg in muscle contributes more than the total observed decrease in whole body glucose disposal in septic rats and that the elevated Rg in skin and intestine partially counteracts the impaired glucose disposal under conditions where the plasma insulin levels are maximally stimulating. (Supported by NIH GM 38032).

85 ROLE OF CALCIUM ON ALTERED GLUCOSE REGULATION DURING HEMORRHAGIC SHOCK. S.R.Maitra*, M.Krikhely*, S.Dulchavsky, E.Geller*, D.J.Kreis,Jr., Div.of Trauma, Dept.of Surgery School of Medicine, State University of New York, Stony Brook, New York 11794.

The effects of hemorrhagic shock (HS) on plasma glucose, lactate, and hepatocyte glucose production were studied. Rats were anesthetized with pentobarbital sodium and both femoral arteries and one femoral vein were cannulated. Rats were bled rapidly to a blood pressure of 40mm Hg and maintained at that level for 2 hours. Blood was withdrawn at pre-shock (PS) and during HS at 30,60,90, and 120 minutes. Rats were divided into groups A and B. At 30 minutes, group B(n=7) received diltiazem (DZ) (1.2mg/kg,i.v.) and group A(n=7) received a saline vehicle. The results indicate:

	Plasma Glucose (mg/dl ± SEM)					Plasma Lactate (mM/L ± SEM)				
	PS	30'	60'	90'	120'	PS	30'	60'	90'	120'
Grp.A	123±12	233±36	257±39	253±42	210±55	2.7±0.5	4.9±1.4	6.8±1.7	5.5±2.1	9.1±1.0
Grp.B	131±11	194±22	130±25	111±20	80±15	1.9±0.2	5.6±1.3	6.9±1.5	7.9±1.3	9.3±1.2

Plasma glucose and lactate increased significantly in both groups A and B at 30 minutes. DZ administration significantly reduced the plasma glucose in group B, whereas plasma glucose in group A remained elevated. Plasma lactate level increased similarly in both groups. Hepatocyte glucose production in surviving rats after 2 hours were 53.7±3.9 uM/g/hr in group A(n=3) and 23.8±3.9 uM/g/hr in group B(n=7). We conclude that during hemorrhagic shock lactate induced glucose production could be prevented by treatment with diltiazem.

86 ALTERATIONS IN BRAIN METABOLISM DURING ACUTE HEMORRHAGIC SHOCK IN RATS: 31P NMR STUDIES. T. McIntosh, T. Yu, V. Head* and R. Vink*. Surgical Research Center, Dept of Surgery, Univ of Connecticut Health Center, Farmington, CT 06032 and Dept. of Biochemistry, James Cook Univ. Townsville, Australia.

Little is known concerning the dynamic metabolic response of the brain to acute hypotensive shock. We evaluated whether phosphorus nuclear magnetic resonance spectroscopy (^{31}P NMR) can detect changes in brain phosphorus metabolism of severely hypotensive rats. Four male Sprague-Dawley rats (n-4) were intubated, anesthetized with isoflurane (1.5%) and instrumented for mean arterial blood pressure (MAP) monitoring. Following skin removal and temporal muscle retraction, a two-turn 5 X 9 mm NMR coil was positioned centrally on top of the skull. 31P NMR spectra were obtained in 10-min blocks for 4 hours on a GE CSI 2T NMR spectrometer using a 90 degree pulse and a 0.5 s repetition rate prior to and following the induction of hemorrhagic shock. After reference spectra were obtained, the animals were bled in the magnet so that the MAP was reduced to 25 mmHg and held constant. Intracellular pH (estimated from the inorganic phosphate (Pi) chemical shift) fell during shock in a manner reflective of the change in blood pH. The phosphocreatine/inorganic phosphate ratio (PCr/Pi) fell significantly by 20 min post-shock ($p<0.05$) and remained suppressed up to 4 hours post-shock (longest survival of any animal). No changes in intracellular ATP were observed. These results suggest that changes in brain metabolism do occur during uncompensated hemorrhagic shock and that NMR can be utilized to dynamically monitor metabolic status of the brain during shock.

87 REGULATION OF GLUCOSE KINETICS IN TRAUMA PATIENTS BY GLUCAGON AND INSULIN. K.M. Nelson, C.L. Long*, W.S. Blakemore*, H.J. Laws*, C. Bergen*, L. Thomas*, and L. Newman*. The Baptist Medical Centers and Carraway Methodist Medical Center, Birmingham, Alabama 35211.

The role of insulin and glucagon as mediators of changes in glucose kinetics in 6 trauma and 5 control patients were evaluated by infusing somatostatin (SRIF). Euglycemia was maintained by infusion of exogenous glucose. Glucose kinetics were measured by the primed-constant infusion of [^{14}C-U,^{3}H-6]glucose and calculated from the Steele equations. The endogenous glucose production rate (Ra) was determined by subtracting the glucose infusion rate from the calculated glucose appearance rate.

TIME	Ra (umol/kg/min)		Rd (umol/kg/min)		INSULIN (uU/ml)		GLUCAGON (pg/ml)	
	Control	Trauma	Control	Trauma	Control	Trauma	Control	Trauma
Basal	8.09	11.87	8.29	13.37	37.2	13.9	218	312
SRIF + 90 m	2.14	4.74	6.67	9.14	20.8	8.0	96	214
SRIF + 180 m	5.61	10.77	7.17	11.28	19.7	8.3	112	215

Basal Ra was increased 47% in trauma subjects. The Ra of trauma subjects decreased to 60% of control basal rates at SRIF + 90 min but was elevated 33% at 180 min. SRIF lowered plasma insulin and glucagon in control and trauma subjects. The return to basal Ra and Rd with continued depression of insulin and glucagon suggest non-hormonal mechanisms (cytokines or post-receptor events) contribute to altered glucose kinetics in trauma. [Supported by NIH Grant # GM 35031]

88 CHANGES IN MYOCARDIAL ENERGY CHARGE FOLLOWING CARDIAC ARREST AND SUBSEQUENT RESUSCITATION. K. Okada, S. Kohri* and H. Kawabata*. Dept. of Anesthesiology, Teikyo Univ. School of Medicine.

Cardiac resuscitation will be difficult as arresting time is prolonged. This study was designed to investigate changes in energy charge(EC) during cardiac arrest and subsequent resuscitation periods. The experiment was divided into 2 parts. The first part: 36 rats were divided into 6 groups. Control rats were anesthetized only with pentobarbital and the heart was extirpated. In other rats, an acute exsanguination was carried out until mean arterial pressure(MAP) fell to 0, and then the rats were divided into 5 groups according to the time of extirpation following cardiac arrest: 1,5,10,15 and 20 minutes, respectively. The extirpated hearts were rapidly frozen with liquid nitrogen. ATP, ADP and AMP were enzymatically measured

and EC was calculated. ECG was monitored to ascertain complete electrical arrest. Disappearance of ECG activity was observed about 9 minutes after MAP reached zero. The second part: 36 rats were also divided into 6 groups. After the same manipulation as in the first part, the extirpated heart was perfused for 30 minutes using Langendorff method and both cardiac function(LVP,LVdp/dt and HR) and EC were investigated. Total adenine nucleotide(TAN) was already diminished at 1 minute and decreased progressively. On the contrary, EC was well maintained around control level until ECG activity disappeared completely, and an abrupt decrease in EC occurred after electrical arrest. When the heart was perfused about 30 minutes, EC was recovered to almost control level in the groups in which perfusion was started within 10 minutes, but its recovery was incomplete in the groups in which perfusion was begun after 10 minutes. TAN was decreased as the arresting time was prolonged.

89 ADENOSINE RECEPTOR MEDIATION OF MYOCARDIAL GLUCOSE UPTAKE DURING ENDOTOXIN SHOCK IN THE DOG. R.M. Raymond, N.F. King*, J. Gordey*, M.E. Person*, J.Radke*, and L.Farkas*. Depts. of Surgery and Physiology, Loyola Univ. Stritch School Med., Maywood, IL and the VA Hosp. Hines, IL.

Recent data have shown that adenosine increased both basal and insulin-stimulated glucose uptake during control and acute endotoxin shock. In skeletal muscle and adipose tissue, various adenosine receptor analogs (A_1 or A_2) had differential effects in mediating glucose transport and metabolism - A_1 stimulation inhibits muscle glucose uptake and potentiates glucose uptake in adipose tissue. The present study was designed to investigate the relationship between A_1- and A_2- adenosine receptors in modulating myocardial glucose uptake during acute endotoxin shock in the dog. Animals were instrumented to measure coronary blood flow and arterial blood pressure. Catheters were positioned to collect coronary sinus and arterial blood for glucose determinations. Myocardial glucose uptake was calculated as the product of coronary sinus - arterial glucose concentration and coronary blood flow. Control animals received either an A_1 (cyclopentyladenosine;CPA) or A_2 (NECA) adenosine receptor agonist infused into the coronary artery for 30 min. prior to collecting blood samples. These agonists were infused sequentially at concentrations between 10^{-11} and 10^{-5} mol/min. CPA demonstrated a dose-dependent increase in myocardial glucose uptake (4.1 to 11.6 mg/min), whereas NECA had no effect on myocardial glucose uptake (4.2 to 3.9 mg/min). CPA had little effect on coronary blood flow at the low concentrations (10^{-11} to 10^{-8}) while NECA increased coronary blood flow from 50 to 112 ml/min. In the endotoxin shock animals (1 mg/kg *S. typhimurium, i.v.*), myocardial glucose uptake decreased from 4.4 to 2.9 mg/min and coronary blood flow decreased from 63 to 44 ml/min. CPA infusion following one hour of endotoxin shock resulted in an increase in myocardial glucose uptake from 2.9 to 11.5 mg/min. These data indicate that the stimulation of the A_1- adenosine receptor mediates increased glucose uptake by the heart and suggest that the decrease in myocardial glucose uptake during endotoxin shock may be related to a diminished adenosine effect. (Supported by NIH Grant HL-31163 and the VA).

90 EFFECT OF COCAINE ON EXTRACELLULAR CALCIUM AND MAGNESIUM HOMEOSTASIS. J. Roa*, G. G. Stanford*, R. Burke*, B. Chernow, Department of Anaesthesia, Harvard Medical School/Massachusetts General Hospital, Boston, MA 02114

The illicit use of cocaine as a stimulant has reached epidemic proportions in the U.S. Many cocaine-intoxicated patients are presenting in circulatory shock after motor vehicle and/or penetrating trauma. Since cocaine is known to cause seizures and ventricular arrhythmias and since calcium channel antagonists block these cocaine-induced problems, we hypothesized that cocaine may alter extracellular calcium (Ca) and/or magnesium (Mg) concentrations. To test this hypothesis, we administered intraperitoneal injections of cocaine in a dose-response manner (placebo, 10, 25, 50 75 and 100 mg/kg) to 325-350 gm male Sprague-Dawley rats (n=6-10 for each group) anesthetized with sodium pentobarbital. We measured blood ionized Ca and serum ultrafilterable and total Mg concentrations by ion selective electrode and colorimetric assays respectively. Blood samples were collected before and 1,5,15,60 minutes after cocaine administration. Blood ionized calcium concentrations did not change from baseline with any of the cocaine dosages at any time points. Serum ultrafilterable and total Mg concentrations were increased ($p<0.05$) following 50 and 75 mg/kg of cocaine relative to pre-injection and to placebo. Due to the anesthesia, no seizure activity was noted; however, cardiac arrest occurred in some rats given 75 or 100 mg/kg of cocaine. We conclude that, within the constraints of our experimental design, single dosages of cocaine fail to change extracellular calcium concentrations. Higher cocaine dosages cause hypermagnesemia and/or cardiac arrest. Repeated daily administration of cocaine may cause different actions on divalent ion metabolism.

91 THE DENERVATED MUSCLE AND MUSCLES OF TRAUMA PATIENTS EXHIBIT SIMILAR CHANGES IN FREE AMINO ACID LEVELS. J. Turinsky and C.L. Long. Albany Med. Coll., Albany, NY 12208 and Baptist Med. Ctrs., Birmingham, AL 35211.

Muscle denervation results in the development of insulin resistance and stimulated net proteolysis in the affected tissue. To test the effect of these alterations on free amino acid levels in muscle, the sciatic nerve was sectioned in one hindlimb of the rats, and intracellular concentrations of 27 free amino acids in the soleus muscles of the denervated hindlimb and the contralateral sham hindlimb were determined 3 days after surgery. The denervation had no effect on the total concentration of free amino acids/l intracellular water. However, the pattern of free amino acids in the denervated muscle was significantly altered. Compared to the sham soleus muscle, the denervated counterpart exhibited increased ($p<0.004$) levels of valine (+38%), leucine (+87%), isoleucine (+79%), glutamate (+74%), and tyrosine (+69%). The denervated soleus muscle also showed decreased ($p<0.03$) levels of glutamine (-56%), glycine (-32%), aspartate (-21%), serine (-49%), alanine (-39%) and citrulline (-53%). It is concluded that insulin resistance and stimulated net proteolysis co-exist with the altered pattern of free amino in the denervated muscle. Since a similar pattern of changes is observed in clinical situations associated with muscle wasting and insulin resistance (severe trauma, major surgery), the denervated muscle may prove to be a useful model for studying mechanisms of muscle amino acid metabolism in recovering surgical patients. (Supported by JDF Grant 188536 and NIH Grant GM 35031.)

EFFECT OF STERILE INFLAMMATION AND SEPSIS ON PYRUVATE DEHYDROGENASE COMPLEX ACTIVITY IN MITOCHONDRIA ISOLATED FROM SKELETAL MUSCLE T.C. Vary, Department of Physiology, Milton S. Hershey School of Medicine, Hershey, PA 17033

The effect of sterile inflammation and sepsis on the proportion of active pyruvate dehydrogenase (PDH) complex in mitochondria isolated from skeletal muscle has been investigated. Total PDH complex in mitochondria from control animals was 69±5 units/g protein, and the concentration of citrate synthase 1083±122 units/g protein. There were no significant differences in either total PDH or citrate synthase activity in either sterile inflammation or sepsis compared to control. The proportion of active PDH in mitochondria from control animals was determined following isolation (44±6%) and was reduced following incubation (5 min) with respiratory substrates (29±2%). In the presence in inhibitors of PDH kinase, the proportion of active PDH was increased to 51±7% with pyruvate and to 78±7% with dichloroacetate. Under all conditions examined there were no differences between control and sterile inflammation. However, the proportion of active PDH in mitochondria isolated from skeletal muscle of septic animals was significantly reduced under every incubation condition examined. Hence, the effects of sepsis to lower the proportion of active PDH complex persists during isolation and incubation of mitochondria in skeletal muscle, even in the presence of inhibitors of the PDH kinase. The results suggest sepsis induces a stable mechanism which inhibits PDH activity. (Supported by NIH GM 36139)

93 EFFECT OF CELLULAR Ca^{2+} MODIFIERS ON SKELETAL MUSCLE GLUCOSE TRANSPORT IN BACTEREMIC RATS. M.V. Westfall and M.M. Sayeed. Dept.of Physiology, Loyola University School Medicine, Maywood, IL 60153.

To determine whether changes in cellular Ca^{2+} contribute to altered skeletal muscle sugar transport in bacteremia, 3-O-methylglucose (3MG) transport was measured in soleus muscles from fasted, male rats given saline (0.5ml,control-C) or bacteria ($4x10^{11}$ Escherichia coli/ kg-B) 12 hrs earlier. Basal and insulin-mediated (10 mU/ml) 3MG transport were measured using ^{14}C-3MG efflux from muscles incubated in a Krebs media, containing various $[Ca^{2+}]_o$ (0.1-5mM) and $[Na^+]_o$ (140,40mM) with or without ionomycin (1μM) or ryanodine (1μM). The altered 3MG transport

	Control (C, x 10^{-2} min^{-1})			Bacteremic (B, x 10^{-2} min^{-1})		
Treatment*	n	Basal	+Insulin	n	Basal	+Insulin
KR media	8	1.849±0.108	5.580±0.201	12	2.341±0.100*	4.106±0.177*
0.1mM Ca^{2+}	8	1.962±0.098	5.328±0.196	8	2.793±0.159*	4.543±0.140*
5.0mM Ca^{2+}	12	2.140±0.065	5.790±0.149	8	2.645±0.139*	4.690±0.185*
Ionomycin	8	3.209±0.263+	3.500±0.216+	8	3.373±0.500+	3.465±0.435+
Ryanodine	8	3.120±0.188+	3.277±0.260+		N.D.	N.D.
40 mM Na^+	8	3.284±0.094+	4.211±0.186+	8	3.683±0.171	4.270±0.308+

*Values=mean+SEM; +p<0.05 vs. untreated C or B; *p<0.05 vs. similar C.

observed with 40mM Na^+ in C but not B muscles suggests a similar degree of altered Ca^{2+} regulation may have previously occurred in B muscles. Ionomycin and ryanodine further altered transport and possibly cellular Ca^{2+} regulation in C and B rat muscles. Support:NIH GM32288 & HL31163.

94 EFFECTS OF NORMOBARIC AND HYPERBARIC OXYGEN (HBO) IN CIRCULATORY SHOCK INDUCED BY SPLANCHNIC ARTERY OCCLUSION AND REPERFUSION IN RATS. Haim Bitterman, Noemi Bitterman*, Yehuda Melamed*, and Leon Cohen*. Shock Research Laboratory, Department of Internal Medicine B, Lady Davis Carmel Hospital, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 34362, and Israel Naval Hyperbaric Institute, Haifa 31080, Israel.

Hyperbaric oxygen (HBO) is an effective therapeutic agent which increases tissue oxygenation. We studied the effects of 100% oxygen at 1ATA (normobaric oxygen), and 2ATA (HBO) in splanchnic artery occlusion (SAO) shock. Pentobarbital anesthetized rats subjected to total occlusion of the superior mesenteric and the celiac arteries for 40 min. developed a severe shock state characterized by hypotension, hemoconcentration, a 6-fold increase in plasma cathepsin D activity, and a uniformly fatal outcome within 80 minutes after the release of the vascular occlusion. Post-reperfusion treatment with either HBO or normobaric oxygen maintained MABP at significantly higher values compared to control air breathing SAO shock rats (final MABP 91±11 at 2ATA, 80±7 at 1ATA, vs 50±5 mmHg in the control group, $p<0.01$). Oxygen treatment attenuated the plasma acummulation of the lysosomal hydrolase cathepsin D ($p<0.05$ at 2ATA), as well as the increase in hematocrit ($p<0.01$ at 2ATA) in a dose related manner. SAO shock rats treated with either normobaric or hyperbaric oxygen exhibited significantly higher survival rates than the SAO shock+air group (77% vs 0% respectively, $p<0.01$), and prolonged survival times ($p<0.01$ from air controls). The data suggest that the beneficial effects of hyperoxia outweigh its possible deleterious effects in splanchnic ischemia and reperfusion.

95 ENHANCED RATE OF SUPEROXIDE ANION GENERATION AMONG CIRCULATING NEUTROPHILS FOLLOWING PSEUDOMONAS AERUGINOSA SEPSIS IN THE PIG.
K.Byrne*, A.Schneider*, D.Carey*, C.Blocher*, A.Fowler*, J.Jenkins*, B.Fisher*, and H.Sugerman. Depts. of Surgery and Medicine, Medical College of Virginia, Richmond, VA 23298.

The superoxide anion burst generated by activated neutrophils is associated with endothelial cell injury in sepsis. We assessed levels of neutrophil activation by measuring kinetics and endpoint production of superoxide anion (cytochrome c reduction at 550 nm, phorbol myristate acetate stimulation) in pre and post pseudomonas infused (Ps,n=5) and NaCl control (C,n=5) pigs. Neutrophils were isolated from blood at 0 and 60 min following a 1 hr infusion of live pseudomonas ($5x10^8$ CFU/ml at 0.3ml/20 kg/min) or 0.9% NaCl. Ps infusion resulted in a significant ($p<0.001$) peripheral neutropenia (78% reduction in circulating PMN at 60 min vs 0 min, viability > 98%) Despite an initial higher burst of O_2^- production (Table), neutrophils from Ps infused animals exhibited 36% less O_2^- generation than controls ($p<0.05$) at the 30 min end point.

Group	0-1 min	1-2 min	2-3 min	3-4 min
Ps (0)	0.00±0.00*	0.15±0.07*	0.52±0.22*	0.75±0.30*
Ps (60)	0.47±0.12	1.67±0.50	1.98±0.44	1.72±0.31

nmoles O_2^-/min/10^6 cells ± SEM, *$p<0.05$ Ps(0) vs Ps(60)

In this neutrophil subpopulation the initial rate of O_2^- production and therefore destructive capacity is increased but overall O_2^- generation is decreased thus diminishing bactericidal capability in these cells in severe sepsis.

96 ENHANCED SUPEROXIDE ANION KINETICS OF PORCINE NEUTROPHILS UPON EXPOSURE TO PSEUDOMONAS AERUGINOSA IN-VITRO. D.Carey*, A.Schneider*, K.Byrne*, C.Blocher*, A.Fowler*, J.Jenkins*, B.Fisher*, and H.Sugerman. Depts. of Surgery and Medicine, Medical College of Virginia, Richmond, VA 23298.

Generation of neutrophil derived short lived oxidants (O_2^-, H_2O_2) is associated with endothelial cell injury in sepsis-induced multisystem organ failure in humans. It is unclear whether live bacteria with an intact cell wall will similarly activate porcine neutrophils. Neutrophils ($1x10^6$ viable cells/ml) from healthy young swine were incubated for one hour at 37°C in stirred cuvettes with live Pseudomonas aeruginosa (Ps) or HBSS buffer (C). The kinetics of superoxide anion generation were measured [cytochrome c reduction at 550nm, phorbol myristate acetate (PMA) 200ng/ml stimulation] and compared.

Group	0-1 min	1-2 min	2-3 min	3-4 min	4-5 min
C (n=5)	0.43±0.14	0.97±0.17	1.04±0.12	1.01±0.08	0.77±0.13
Ps (n=5)	1.97±0.25*	2.25±0.18*	1.90±0.12*	1.82±0.01*	1.66±0.14*

nmoles O_2^-/min/10^6 cells ± SEM, *p<0.001 Ps vs C

Neutrophils exposed to live Ps exhibited 93.5% greater total O_2^- generation (Ps, 15.8±1.1 vs C, 8.15±1.1 nmol $O_2^-/10^6$ cells, mean ± SEM, $p<0.01$) than controls at the ten minute endpoint. These cells also demonstrated a significant increase in the rate of superoxide production (Table). The results show the enhanced capability of activated porcine neutrophils to produce toxic oxygen species when exposed to live Pseudomonas. Thus porcine neutrophils in sepsis exhibit similar superoxide anion kinetic characteristics to humans.

97 HEMORRHAGIC SHOCK INDUCED HEPATOCELLULAR DAMAGE, PREVENTABLE BY DEFEROXAMINE. D.W. Griffin and C.F. Babbs Hillenbrand Biomedical Engineering Center, Purdue University, W. Lafayette IN 47907

The importance during hemorrhagic shock of reperfusion injury associated with hydroxyl radical generation by the iron catalyzed Haber-Weiss reaction is still uncertain. To examine the role of iron in mediating hepatocellular damage during reperfusion after hemorrhagic shock, we studied three groups of n==3 dogs each bled so as to reduce mean arterial pressure to 40 mmHg (+/- 5mmHg) for three hours and subsequently treated 20 minutes prior to reinfusion of shed blood with either 0.9% saline, 5ml/kg (Group 1); deferoxamine, 50mg/kg in 0.9% saline (Group 2); or 6% pentastarch solution, 5ml/kg (Group 3). Serum alanine aminotransferase (ALT), a specific marker for hepatocellular injury in the dog, was measured as an indicator of hepatic reperfusion injury. During shock, ALT did not change significantly from the normal in in any group. After reperfusion, however, ALT rose in Groups 1 and 3 from a mean baseline value of 17 +/- 7 U/L to a post-reperfusion plateau of 5700 +/- 2200 U/L, group 1, and 3700 +/- 1300 U/L, group 3, in three hours in a pattern suggesting hepatic reperfusion injury. Deferoxamine treated dogs, however showed significantly smaller elevations in ALT after transfusion to only 600 +/- 320 U/L ($P<.025$). Mean arterial pressures in Group 2 were not significantly different from those in Groups 1 and 3. These early findings suggest that deferoxamine preventable reperfusion injury of the liver, perhaps involving the Haber-Weiss reaction, may play a role in the pathophysiology of hemorrhagic shock.

98 ROLE OF FREE RADICALS IN KUPFFER CELL EXACERBATION OF HEPATOCYTE REOXYGENATION INJURY. S. Kobayashi*, M. Clemens. Johns Hopkins Sch. Med., Baltimore, MD 21205.

We have previously reported that the presence of Kupffer cells exacerbated hepatocyte reoxygenation injury. The present study was undertaken to investigate whether free radicals contribute to this injury. Cultured hepatocytes (H) were incubated ± Kupffer cells (K) during 90 min hypoxia plus 90 min reoxygenation. Free radicals were scavenged with superoxide dismutase + catalase (SOD). These results were compared to the effect of SOD on cell injury produced by addition of xanthine oxidase + hypoxanthine (XO). Cell damage was estimated by lactate dehydrogenase (LDH) release reported as % total LDH. *p<0.05 vs H **p<0.05 vs H, H+XO+SOD

(rats/replicates)		anoxia		reoxygenation		
		0	90	30	60	90
H	(6/24)	9.0+1.3	16.6+2.4	19.4+2.1	19.6+2.3	20.8+2.2
H+K	(6/24)	10.9+1.5	19.8+2.2	26.9+2.1*	27.1+1.9*	28.7+2.2*
H+K+SOD	(6/24)	10.5+1.8	20.6+1.8	24.9+2.3	25.3+1.8	25.9+1.9

H	(3/12)	9.4+3.3	16.1+2.6	18.3+3.8	19.0+3.2	19.7+0.8
H+XO	(3/12)	11.4+1.1	24.7+3.2**	32.7+3.9**	34.6+3.2**	46.2+3.3**
H+XO+SOD	(3/12)	10.3+5.4	15.8+4.7	18.2+5.2	22.2+2.5	24.6+5.6

Thus, SOD + Cat virtually prevented free radical (XO) injury but not Kupffer cell injury. Although free radicals may contribute to reoxygenation injury, our results suggest that they are not responsible for the Kupffer cell-induced injury. Supported by NIH DK 38201 and the Robert Garrett Fund.

99 DMPO DOES NOT TRAP FREE RADICALS IN VIVO DURING SEPSIS. S. A. Lloyd * and P. B. McCay*, (Spon: L. Hinshaw) OK Med. Res. Found., Oklahoma City, OK 73104

In vitro studies suggest oxygen-centered free radicals may be produced by macrophages and neutrophils during sepsis. The use of 5,5-dimethyl-1-pyrolline N-oxide (DMPO) in models of septic shock in vivo is increasing due to the affinity of this spin trap for oxygen-centered free radicals and successful experience with DMPO in vitro. We examined the generation of free radicals in a rat model of septicemia using DMPO administered i.p. or i.v. before, during or after E. coli lipopolysaccharide (LPS) i.v. or i.p. Liver and/or heart were processed for electron paramagnetic resonance (EPR) spectroscopy using Folch or chloroform extraction procedures. No radicals were trapped when distilled DMPO was used, while EPR spectra indicating the trapping of carbon-centered radicals were observed in 4 of 18 LPS-treated rats and 2 of 18 controls treated with filtered DMPO. Spectra similar to these can be generated during homogenization of tissues incubated with filtered DMPO but not experimentally exposed to LPS. No EPR spectra were observed in experiments using the spin traps trimethoxy-α-phenyl-N-tert butylnitrone (n=3) or α-phenyl-N-tert butylnitrone (n=4). These data suggest cautious interpretation of results from in vivo studies involving DMPO. Continued research using alternative spin traps and methods for tracking free radicals in vivo may better elucidate the role of free radicals in sepsis.(supported by NIH Grants GM36512 and GM08237).

100 WHICH ONE ACCOUNTS FOR THE LUNG INJURY INDUCED BY OLEIC ACID, PMN OR XOD? Z. Y. Luo, Q. Y. Zhou* D. K. Song* Y. Tan* Dept. of Pathophysiology, Hunan Medical University, Changsha, Hunan, People's Republic of China.

Three lines of investigation indicated that O_2 radicals (ORs) originating from X/XOD account in part for lung injury. First, rats were pretreated with tungsten (W), an inhibitor of XOD. A tungsten enriched diet (protein impregnated with 0.7 g/kg sodium tungstate) was given in H_2O 10 ppm W for 3 weeks. Rats fed with ordinary diet served as controls. The lung was isolated, ventilated with 95% O_2/5% CO_2 and perfused with Kreb-Henselet solution. The levels of MDA and SOD of perfusate were measured 30 min after OA injection. Rats pretreated with W had less changes of MDA and SOD: MDA (uM/ml) 0.30 ± 0.02 vs 3.37 ± 0.03, P 0.01; SOD (u/ml) 2.80 ± 0.24 vs 4.59 ± 0.30. Second, rats were pretreated with W mentioned above, but the lung was injured with injection of OA (in the presence of blood component). The results showed that there is still a difference between two groups. In the W pretreated group, there is higher WBC total count in blood (115.05 ± 10.44 vs 76.12 ± 5.07% of baseline 5 min after OA injection, P 0.01), less WBC infiltration in lung tissue and lower level of lung coefficiency (8.97 ± 0.58 vs 12.31 ± 0.34, P 0.01). Third, Cultured Bovine Pulmonary Endothelial Cells can be damaged by exogenous X/XOD: LDH (u/ml) 4.21 ± 0.30 vs 2.10 ± 0.45 control; MDA (uM/ml) 0.24 ± 0.02 vs 0.14 ± 0.03 control, P 0.01. In conclusion: 1) Lung injury induced by OA is mediated in part by ORs; 2) ORs might be generated by X/XOD rather than by PMN in the presence of blood component; 3) Even in the presence of blood component, ORs originated from X/XOD might play a primary role in inducing lung injury.

101 NEUTROPHIL CATHEPSIN-G (CATG): A POTENT DISRUPTOR OF HUMAN ENDOTHELIAL MONOLAYERS. D. Magnuson*, and R. Maier. University of Washington, Seattle, WA, 98195.

The release of neutral proteases from activated neutrophils(PMNs), resulting in endothelial injury, barrier disruption, and increased permeability, is thought to contribute to acute organ dysfunction, both in the lung and elsewhere, during sepsis syndrome. PMNs contain two neutral proteases in large quantities: elastase(ELA) and CATG. Elastase has been implicated in chronic lung diseases (eg. emphysema), but the primary effector of acute pulmonary pathology during sepsis remains obscure. We studied the effects of CATG and ELA on human endothelial monolayer integrity to assess their potential roles in the pathophysiology of acute lung injury in sepsis. Human umbilical vein endothelium(HUVE) was exposed to human PMN-derived CATG and ELA, as well as bovine pancreatic DPCC-treated trypsin(TRP) in the absence of serum. Undetached HUVE were stained with crystal-violet, and dye uptake quantitated spectrophotometrically at 550 nm. Concentrations (μg/ml) effecting 50% release (EC_{50}) were calculated and efficiencies(EF) expressed relative to TRP (TRP=1.0):

EXP	EC_{50}(CATG)	n	EC_{50}(ELA)	n	EF(CATG)	EF(ELA)	EF(CATG)/EF(ELA)
1	4	6	12	6	2.0	0.67	3.0
2	40	6	500	6	0.5	0.04	12.5
3	4	6	100	6	0.5	0.02	25.0
4	8	6	20	6	0.25	0.1	2.5
5	4	6	20	6	2.5	0.5	5.0

CATG was more efficient in disrupting HUVE monolayers than ELA by a ratio of 2.5-25.0 (mean = 9.5), and as effective as TRP (mean EF(CATG) = 1.1). We conclude that CATG is highly effective in disrupting endothelial integrity *in vitro*, and may have a significant role in PMN-induced barrier injury during sepsis.

102 **COMPARATIVE STUDY OF FREE RADICAL INJURY OF VARIOUS ORGANS IN RATS DURING SEPSIS.** Xian Jun Meng, Ping Zhang*; Institute of Basic Medical Science Research, General Hospital of PLA Beijing, China

Septic responses may ultimately lead to sequential failure of organs diverse anatomically and physiologically from each other. Previous study from this lab demonstrated that liver plays a central role in the development of multiple organ failure. This is a comparative study of the generation, injury, and scavenge of oxygen-derived free radicals in different organs of rats during sepsis. Rats weighing 200-250 g of either sex were used. Animals were sacrificed 10 hr after the ligation and perforation of caecum. Tissues from liver, kidney, lung, and small intestine were removed and assayed for:- lipoperoxide(LPO); xanthine oxide(XOD); catalase(CAT); GSH-peroxidase(GSH-Px); and glutathione(GSH). Results showed that liver is the only organ with significant increase of LPO concentration, (38.9±2.0 - 72.9±3.7 nmoles/g; $p/0.001$). The XOD activity increased in liver (312.12±13.03 - 435.28±14.9 nmoles/g; $p/0.001$), and lung (228.23±10.85 - 299.33± 8.19 nmoles/g; $p/0.001$). The CAT activity decreased only in liver (54.42±1.69 - 45.00±2.19 K/g; $p/0.01$). The concentration of GSH decreased in all the four organs examined but the diminution is most profound in liver, reached 50% of that of control(242.6±17.3 - 123.4±7.3 ug/100mg). These findings indicate that liver is the first target of oxygen-derived free radical injury, and may provide another evidence as to the critical role liver plays in the development of multiple organ failure.

103 THE EFFECTS OF OXIDATIVE STRESS ON RAT PROXIMAL TUBULAR EPITHELIUM (PTE): A ROLE FOR CYTOSOLIC CALCIUM ($[Ca^{2+}]_i$). N. Nitta*, A. Maki*, M. Smith*, P. Phelps*, K. Elliget*, I. Berezesky* and B. Trump. Maryland Institute for Emergency Medical Services Systems and Dept. of Path., U. of MD School of Medicine, Balto., MD 21201

Oxidative stress from a variety of sources, including PMN infiltrates and reperfusion injury appears to be a significant source of cell injury in shock. We investigated this in cultured rat PTE using the xanthine/xanthine oxidase (X/XOD) system. This system generates $O_2^{\cdot-}$ and H_2O_2 extracellularly which reacts first at the cell surface. Cell viability was measured after exposure to serum-free medium containing xanthine (500 μM) and XOD (2.5-25 mU/ml) for 1, 2 and 3 hr by using the neutral red (vital dye) assay and presented as % of control. Viability at 1, 2 and 3 hr following 5 mU/ml XOD was 71, 48 and 36%, respectively. X/XOD caused time- and dose-dependent decreases in viability. Pre-addition of catalase protected the cells

significantly; however, superoxide dismutase had only a slight protective effect. Changes in $[Ca^{2+}]_i$ following X/XOD (25 mU/ml) were determined by spectrofluorometric measurement of Fura 2-loaded cells. In the presence of normal $[Ca^{2+}]_e$ (1.37 mM), there was an initial rapid transient increase in fluorescence followed by a slower secondary sustained increase. The initial $[Ca^{2+}]_i$ increase which was observed in normal $[Ca^{2+}]_e$ was not seen with low $[Ca^{2+}]_e$ (< 5 μM). The transient increase was prevented with low $[Ca^{2+}]_e$ but the sustained increase was not. These data suggest that both influx of Ca^{2+} (early transient) and redistribution of Ca^{2+} from intracellular stores, e.g. mitochondria and ER (secondary sustained) play a major role in the deregulation of $[Ca^{2+}]_i$. [NIH AM15440 and Navy N00014-88K-0427.]

104 COMPLEMENT ACTIVATION: EFFECT ON RED BLOOD CELL DEFORMABILITY. R.J. Powell*, G.W. Machiedo, B.F. Rush Jr*, and G.Dikdan* N.J. Med. Sch., Newark, NJ,01703

We have previously demonstrated that red cell deformability (RCD) is decreased during sepsis and this may lead to impaired oxygen utilization and microcirculatory flow. The purpose of this study was to evaluate the effect of complement activation on RCD and the role of oxygen free radicals in this pathologic process. Zymosan (zym) a potent activator of the alternate complement pathway was used to activate complement, alpha tocopherol (AT) was used as a free radical scavenger. Male Sprague-Dawley rats were randomized to the following groups: CONTROL (n=7) ; Z60 (n=8) 60 mg/100g zym IP ; Z100 (n=6) 100mg/100g zym IP; AT/Z60 (n=4) and AT/Z100 (n=4). AT groups were pretreated with AT 4mg/100g SQ x 3 days and .5mg/100g IV prior to zym. Animals were sacrificed 90 minutes following zym injection ; red cell deformability index (DI) and conjugated dienes, a byproduct of lipid peroxidation, were measured.

Results:

	CONTROL	Z60	Z100	AT/Z60	AT/Z100
DI	.88±.05	.75±.09*	.66±.22#	.98±.15	.90±.13

*=p<.01 compared to CONTROL and AT/Z60, #=p<.01 compared to CONTROL.(ANOVA) Regression of DI as a function of conjugated diene levels disclosed a correlation coefficient of -.695 (n=20, p<.001). Activation of complement resulted in a significant inverse correlation between increased lipid peroxidation byproducts and decreased RCD . Normal RCD was maintained despite complement activation, by pretreatment with the anti-oxidant AT. Free radicals are likely mediators in the decreased RCD during complement activation.

105 NOREPINEPHRINE (NE) INDUCED ATERATIONS IN LIPID PEROXIDATION (LPO):INTACT RATS VS. HEPATOCYTES. M.QI*, C-S.TANG, J-Y.SU (Sponsor: Stephen B. Jones)
DEPARTMENT OF PATHOPHYSIOLOGY, BEIJING MEDICAL UNIVERSITY CHINA

Circulatory shock is associated with both marked LPO and elevated plasma catecholamines. We studied the interaction of these alterations in non-shock states by comparing the effect of exogenous NE in intact rats with that in hepatocyte preparations. Fasted male rats anesthetized with Urethane were infused with NE (7.4nM/100g B.W./min,) for 40 min and then arterial plasma was collected. Plasma cathepsin D and Lactic dehydrogenase (LDH) activities increased 1.45- and 1.13-fold, respectively, and malondialdehyde (MDA) content, (an index of LPO), increased (14.6%), suggesting that exogenous NE induced LPO and tissue injury. To test if the action of NE was direct, rat hepatocytes were incubated with NE and free radical generating system (FRGS), Fe^{++} and ascorbic acid. The increase in cellular MDA content induced by FRGS was inhibited 41.4%($p<0.01$) by 10 μM NE. FRGS-induced cellular damage was also reduced in that both leakage of cytoplasmic enzyme LDH and the increase of intracellular Ca^{++} content was decreased. The inhibition of LPO in hepatocytes by NE was dose dependent, with no inhibition below 0.1 uM NE. These data suggest that NE in the intact rat results in stimulation of LPO via vasoconstrictor action, while NE directly inhibits LPO at the cell membrane.

106 LIPID PEROXIDATION IN THE LYMPH DURING HEMORRHAGIC SHOCK IN THE RAT.
S. Rose*, J. Dike*, R. Koch*, V. Bühren, G. Harbauer*, O. Trentz.
Depts. of Experimental and Trauma Surgery, University of Saarland, 6650 Homburg, FRG

During ischemia-reperfusion the lymphatic pathway seems to contribute to the development of tissue damage of the lung. In a rat model of aortic cross clamping (ACC) after severe hemorrhage we compared conjugated dienes (CD) in lymph and plasma originating from the lower body. Methods: 20 male Lewis rats (BW 300-330 g); pentobarbital (60 mg/kg BW) i.p.; catheterization of the left carotid artery and of the suprahepatic caval vein; laparotomy and cannulation of the thoracic lymph duct subdiaphragmatically. Shock group: 0-30' withdrawal of 2.5 ml blood/100 g BW; 30-45' 10 ml Ringer's lactate (RL); 45-60' supraceliac aortic cross clamping; 60-180' reperfusion and 10 ml RL/h. Retransfusion of shed blood 55-60' = 30%, 60-75' = 70%. Sham group: no hemorrhage, no clamping, but RL-infusion as in the shock group. Blood samples in 30-min-intervals, lymph samples in 15-min-intervals.
Results: mean concentration of CD during reperfusion (O.D. at 233 nm/µg lipid):

	Lymph	Plasma
Sham	2.75 ± 0.3*	2.95 ± 0.3
ACC	5.27 ± 0.7	2.97 ± 0.2

mean ± SEM; *: $p < 0.005$ (Student's t-test)
Conclusion: In contrast to the plasma collected from the suprahepatic caval vein, the thoracic duct lymph showed a significant rise in lipid peroxidation products during reperfusion. This demonstrates that lymph is a vehicle for oxygen free radical derived products. Bypassing the liver by the lymphatic route these substances reach the lung via the superior caval vein without prior detoxification.

107 THE ROLE OF TUNGSTEN AND ALLOPURINOL IN ATTENUATION OF ISOLATED PERFUSED RAT LUNGS INJURY INDUCED BY OLEIC ACID. D. K. Song*, Z. Y. Luo. Dept. of Pathophysiology, Hunan Medical University, Changsha, Hunan, People's Republic of China.

The aim of this study is to assess whether lung injury induced by Oleic Acid (OA) can be attenuated by Tungsten (W), an inhibitor of xanthine oxidase (XOD) by competition with MO in XOD. Isolated Wistar rat lungs, ventilated with 95% O_2/5%CO^2 and perfused with Kreb-Hensenlet solution, were divided into 4 groups: I. Control group (n=6); II. OA group (n=9)0.007-0.008ml/each; III. OA+W group (rats were pretreated with tungstate sodium salt enriched diet; protein impregnated with 0.7g/kg sodium tungstate was given in H_2O 10ppm W for 3 weeks. Rats fed with ordinary diet served as controls (n=9). IV. OA+Allopurinol ($2x10^{-5}$M, n=9). The following parameters were monitored at 30 min after OA infusion. Results are listed below.

	Pulm. Coefficiency	LDH U(U/ml)	MDA (nM/ml)	SOD (U/ml)
I. Control gp	0.00 ± 0.00	17.3 ± 4.60	0.283 ± 0.01	5.89 ± 0.17
II. OA gp	25.24 ± 2.49++	71.6 ± 7.4++	0.383 ± 0.02++	2.79 ± 0.23++
III. OA+W gp	6.87 ± 1.34**	38.0 ± 5.2**	0.310 ± 0.01**	4.49 ± 0.20**
IV. OA+ALLOP gp	8.76 ± 2.21**	34.7 ± 4.7**	0.318 ± 0.01	5.00 ± 0.37**

Values were mean SEM Vs group I, ++=p 0.01, VS group II, **=p 0.01
In conclusion: 1. Oxygen Radicals (ORs) are mediators in inducing lung injury induced by OA; 2. In the absence of blood component, Ors might be generated by X/XOD system in pulmonary endothelium.

108 ROLE OF COMPLEMENT, HISTAMINE AND XANTHINE OXIDASE IN OXYGEN-RADICAL-MEDIATED MICROVASCULAR INJURY POST BURN. G.O. Till, H.P. Friedl, P.A. Ward, O. Trentz. Univ. of Michigan, Ann Arbor, MI 48109-0602 and Univ. of Saarland, D-6650 Homburg, FRG.

Systemic complement activation (with generation of C5a) and skin edema formation in thermally injured rats are mediated by oxygen radicals derived from xanthine oxidase (X.O.). We now have obtained evidence to suggest that histamine plays a critical role in modulating plasma X.O.-activity. Postburn plasma samples revealed a striking increase in X.O.-activity paralleled by an increase in plasma histamine levels as determined by RIA. X.O.-activity in plasma showed a 4-fold increase peaking at 15 minutes post thermal injury ($p<0.01$). Histamine levels peaked at the same time point demonstrating a 6-fold increase in

comparison to sham animals ($p<0.001$). Plasma xanthine dehydrogenase (X.D.) levels remained unchanged. The dose-dependent, potentiating effect of histamine on X.O.-activity could be duplicated in vitro. Early excision of burned skin or depletion of complement in experimental animals prior to thermal injury significantly attenuated the increase of both histamine and X.O.-activity in postburn plasma. Similarly, after pretreatment of thermally injured rats with cromolyn sodium, the plasma X.O.-activity remained at background levels. Edema formation in burned skin was significantly attenuated following complement depletion or cromolyn treatment of experimental animals. These data suggest that histamine can affect edema formation in thermally injured skin by modulating X.O.-activity. [Supported in part by grants from the NIH (GM39397, GM28499, GM29507) and the DFG (FR744/1-1)].

109 ERYTHROCYTE LIPID PEROXIDATION, ALTERATIONS OF MEMBRANE PROPERTIES AND DEFORMATION IN ENDOTOXIN SHOCK IN DOGS. A. Zhang*and Q.F.Huang* (Spon : B.M.Altura). Beijing College of Trditional Chinese Medicine, Beijing 100013, P.R.China

It has been suggested that lipid peroxidation may be an important factor in endotoxemia. We therefore decided to investigate whether this dose indeed play a role in endotoxin shock. Dogs were treated with E.Coli endotoxin (1.5mg/Kg body weight) by vein injection. Before and 6 hours after injection, blood from endotoxemic dogs was obtained to determine erythrocyte membrane lipoperoxide concentration (as indicated by an increase in malondialdehyde content), membrane fluidity, activity of enzymatic scavengers (SOD, glutathione peroxidase and catalase) and deformation. A significant elevation of lipoperoxide concentration and membrane microviscosity (1/fluidity), and a reduction of erythrocyte deformbility were observed. However, activity of enzymatic scavengers was not altered. There appeared to be inverse correlations of membrane lipoperoxide to membrane fluidity or deformability. Our data suggest that, in endotoxin shock, accumulation of erythrocyte membrane lipoperoxide suggests an increase of free radical production occurred, resulting in membrane disorganization and stiffenning of red blood cells which probably contributes to the hemorrheological disorders seen in shock states.

110 CHANGES OF GSH METABOLISM IN HYPOPERFUSION AND SEPSIS. Ping Zhang*, Xian-Jun Meng. Institute of Basic Medical Science Research, General Hospital of PLA, 28, Fuxing Road, Beijing, China.

GSH is one of the primary molecules in living cells. It plays a key role in cellular protection and metabolic regulation. Changes of GSH and related metabolites in rat liver, kidney and lung were measured in hypoperfusion (MAP 30mmHg,4h) and sepsis (CLP,10h). The results showed: GSH decreased in liver and kidney in hypoperfusion (232±17-170±8 ug/100mg, $P<0.01$; 123±5-103±5 ug/100mg, $P<0.05$) and sepsis (238±13-132±8, 136±3-99±5 ug/100mg, $P<0.001$). ATP and energy charge also decreased significantly in liver and kidney in both conditions. LPO increased in liver in sepsis (44.0±6.9-72.9±3.7 nmoles/g, $P< 0.01$). Concentration of lactic acid in arterial blood increased in hypoperfusion (1.03±0.08-8.95±0.68 mmoles/L) and sepsis (1.14±0.15-2.88±0.32 mmoles/L, $P< 0.001$).

Synthesis of GSH depends on ATP and cellular redox state. Decrease in ATP and energy charge as well as increase in glycolytic activity may inhibit the synthesis of GSH. In addition, scavenging of free radicals accelerates the consuming of GSH. Depletion of GSH compromises cellular anti-injury function and results in metabolic disorder. Hence, it may play an important role in cellular damage in process of multiple organ failure.

111 FLOW-DEPENDENT HEPATIC OXYGEN CONSUMPTION IN EXPERIMENTAL PERITONITIS. D.Arvidsson*,P.Almqvist*,I.Rasmusen* and U.Haglund. Uppsala Univ., Uppsala, SWEDEN.

Earlier studies have indicated that total body hypoxia would not be an important

factor in early sepsis. However, regional differencies are likely to occur. An increase in cardiac output (CO) in the hyperdynamic phase may lead to increased oxygen consumption ($\dot{V}O2$) in some patients suggesting local flow-dependent hypoxia. The aim of this study was to measure liver $\dot{D}O2$ and $\dot{V}O2$ in sepsis (fecal peritonitis). Methods: 10 anesthetized pigs on controlled ventilation were divided in two groups: peritonitis (P,n=5) or control (C,n=5). Cardiac output and portal venous blood flow (thermodilution), hepatic arterial flow (Transonic flowmeter), continuous oxygen saturation (sO2) of pulmonary arterial, portal and hepatic venous blood (fiber oximetry catheters) were measured. Hepatic $\dot{D}O2$ and $\dot{V}O2$ were calculated.

Results:		CO(L/min)	$\dot{D}O2$(ml/min)	$\dot{V}O2$(ml/min)	O2-extr.	sO2(v.hep)%
	0h	2.50±0.33	138±28	36±14	26%	62.6±5.8
C	2h	2.54±0.67	144±34	45±20	31%	57.0±12.4
	4h	2.38±0.57	122±14	48±23	39%	48.4±18.0
	0h	2.51±0.45	150±19	49±18	33%	55.6±4.7
P	2h	1.46±0.30*	122±18	107±19*	88% *	9.6±7.2*
	4h	1.31±0.28*	62±09*	53±11	85% *	6.6±3.6*

* indicates p<0.05 versus corresponding control.

Conclusion: Sepsis induced by fecal peritonitis lowers cardiac output and oxygen delivery while oxygen consumption increases in the liver thus rapidly rendering the hepatic oxygen consumption flowdependent.

112 HEPATOCYTES RELEASE CSF-LIKE FACTORS. P. Bankey,* J. Fulco,* J. Mazuski,* M. Ortiz,* A. Carlson,* F. Cerra. Dept. of Surgery, Univ.of Minn., Mpls., Minn. 55455.

The CSF's are a family of hematopoietic growth factors that regulate macrophage proliferation and activation. Since CSF levels are increased following exposure to endotoxin (LPS) we investigated the effect of GM-CSF on Kupffer cell (KC) interleukin-1 production and proliferation. Murine KC's were obtained by liver perfusion. IL-1 activity was assayed using the D10. G4.1 bio-assay. KC proliferation was assessed by 3H-thymidine incorporation and quantitation of phagocytic cells using fluorescent latex beads. We observed that GM-CSF (500 units, rmGM-CSF, Genzyme) signaled a small amount of IL-1 release compared to control KC's(4.0 +/-0.2 vs.0.3+/-0.1 munits/100ul); however, it primed the KC's for significantly increased amounts of IL-1 following LPS stimulation compared to media alone (23.6+/-3 vs. 44.3+/-5 munits/100ul). In separate experiments, GM-CSF induced progressive proliferation of KC's over 7 days in vitro as measured increased incorporated 3H-thymidine (3 fold) and by fluorescent microscopy. Additional investigations of hepatocyte-kupffer cell communication during in vitro co-culture have similiarly demonstrated proliferation of KC's in co-culture, and that hepatocyte supernatants alone are capable of signaling proliferation and priming the KC's for augmented IL-1 release. We speculate that hepatocyes may produce CSF-like factors that regulate KC proliferation and cytokine production, and that KC hyperplasia may have a role in altered hepatic metabolism during endotoxemia.

113 HYPOXIA-REOXYGENATION AND TNF-α TRIGGER INDEPENDENT PATTERNS OF PROTEIN SYNTHESIS IN HUMAN HEPATOBLASTOMA CELLS. T.G. Buchman and D.E. Cabin*, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD 21205.

Recovery from circulatory shock requires homeostatic responses to protect not only individual cells (internal defenses) but also the integrated organism (systemic defenses). These defenses may share only one of three relationships. Either they are coincident and indistinguishable; they are distinct but share some elements; or they are independent. To selectively stimulate these defenses, HepG2 cells were challenged by heat-shock; by hypoxia-reoxygenation; by IL-1; and by TNF-α. After labelling with either ^{35}S-methionine or $^{32}PO_4$, cellular and secreted proteins were analyzed by one-and two-dimensional electrophoresis. Analysis showed that (1) the internal defensive response to hypoxia-reoxygenation was indistinguishable from the heat-shock response and consists of the synthesis of 34 distinct cellular proteins without apparent secretion into the medium; (2) both IL-1 and TNF-α trigger decreases in two and increases in four secreted proteins including an increase in one of only four phosphoproteins; (3) secretion of IL-1 and TNF-α stimulated proteins is so rapid that the cell lysates were indistinguishable from controls and in particular heat shock proteins were not observed; (4) the responses to TNF-α and

IL-1, while similar, are distinct with respect to the secretion of two proteins, 23.5 kD and 28.5 kD. Recovery from shock may demand simultaneous defenses, particularly for the hypoxic hepatocytes located near hepatic venules. If both responses cannot occur simultaneously within a single cell, the more primitive internal preservation response would likely outrank systemic preservation. An organ-wide shift to internal defense would correspond clinically to organ failure.

114 THROMBOTIC THROMBOCYTOPENIA AND THE ANTI-COAGULANT PATHWAY. R.Catlett* and F.Taylor
Oklahoma Medical Research Foundation, Oklahoma City, OK 73104

Thrombotic Thrombocytopenic Purpura (TTP) is a rare disease of unknown etiology characterized by a triad of consumptive thrombocytopenia, microangiopathic hemolytic anemia and central nervous system dysfunction. Fibrinogen concentrations are usually not decreased. The following studies were undertaken to evaluate the role that the anti-coagulant proteins C and S might play in this disease. Two baboons were treated on Day#0 with the murine monoclonal antibodies HPC-4 and S-163. HPC-4 prevents the activation of protein C. S-163 prevents the binding of C to its cofactor S. On Day#1 a 120 minute infusion of low dose E.Coli was given. Each animal subsequently developed a transient drop in platelets and haptoglobin with a modest drop in hematocrit and rise in creatinine. Fibrinogen concentrations remained at baseline. A further animal was treated with the same protocol but with the addition of intradermal E.Coli on Days#0 and 1. A similar but accentuated pattern of changes took place with platelets dropping to 5% of baseline and the development of severe microangiopathic hemolytic anemia and marked renal dysfunction. Monoclonal antibody control animals and E.Coli control animals did not develop these findings. This evidence suggests that in the presence of an inflammatory state a deficiency of the anti-coagulant proteins C and S may lead to the development of a syndrome consistent with TTP.

115 ALTERATIONS IN BINDING OF INOSITOL 1,4,5-TRISPHOSPHATE (IP_3) TO SUBCELLULAR STRUCTURES OF RAT LIVER DURING CHRONIC ENDOTOXEMIA. I.V. Deaciuc and J.A. Spitzer.
Department of Physiology, Louisiana State University Med. Ctr., New Orleans, LA.

Our earlier experimental work revealed alterations of Ca^{2+}-dependent transmembrane signaling mechanisms in liver during chronic endotoxemia (Metabolism 36, 753, 1987; Am. J. Physiol. 251, R984, 1986). These included a decrease of IP_3-dependent Ca^{2+} release from intracellular stores in permeabilized rat hepatocytes (Am. J. Physiol 253, E130, 1987). The present study was undertaken to further elucidate the mechanism(s) of such perturbations. Male rats were chronically treated with E. coli endotoxin (ET, 0.1mg/100g b.w./24h for 30h) via subcutaneously implanted osmotic minipumps. Control animals received sterile saline from the same type of pumps. Liver plasma membrane (PM) and an endoplasmic-reticulum enriched fraction (ER) were isolated and their ability to bind [^{3}H]IP_3 and to take up and release Ca^{2+} measured. ET treatment significantly reduced [^{3}H]IP_3 binding by both fractions (by 62%) without affecting the corresponding affinity constants. Also, ET treatment decreased the IP_3-dependent Ca^{2+} release by both fractions (48% for ER and 50% for PM) as well as ATP-dependent Ca^{2+} uptake (39% for ER and 50% for PM). Additionally, ET treatment was associated with a significant diminution (by 19%) of 5'-nucleotidase activity of the PM fraction. The results suggest that previously observed impairments in the ability of hepatocytes to mobilize Ca^{2+}, to activate glycogen phosphorylase and to respond - when saponin-permeabilized - by Ca^{2+} release to an IP_3 challenge are partly due to a decrease in the amount of IP_3 binding sites of subcellular fractions that are imputed to be targets of IP_3. Supported by NIH grant GM 30312.

116 **INTERSTITIAL FLUID ACCUMULATION IS CONFINED TO THE LUNG DURING EARLY SEPSIS** G.A. Fantini, S. Shiono* and G.T. Shires* Cornell University Medical College, New York, NY 10021.

Sepsis is accompanied by an increase in extravascular lung water (EVLW), however it is uncertain whether this fluid accumulation is

confined to the lung or occurs throughout the interstitium. EVLW and total body extracellular fluid volume (ECFV) were measured in 6 dogs receiving 1.5 X 10^{10} CFU of live E. Coli intraarterially. Four dogs underwent volume loading only and served as controls. EVLW (ml/kg) was determined by thermal-green dye double indicator dilution method. ECFV (% body wt) was measured by $Na_2{}^{35}SO_4$ isotope dilution technique.

	Baseline	3 Hrs	24 Hrs	48 Hrs
EVLW-SEPSIS	6.2 ± 0.4	7.1 ± 0.2	8.1 ± 0.4*	8.6 ± 0.5*
EVLW-CONTROL	6.1 ± 0.8	7.9 ± 0.9	5.4 ± 0.2	6.9 ± 0.3
PCWP-SEPSIS	5.4 ± 0.2	7.3 ± 1.7	6.0 ± 0.9	4.4 ± 0.6
PCWP-CONTROL	5.5 ± 0.9	10.3 ± 0.5#	8.0 ± 1.5	5.0 ± 1.5
ECFV-SEPSIS	15.2 ± 0.6	---	---	14.6 ± 1.0
ECFV-CONTROL	15.1 ± 0.4	---	---	15.4 ± 1.0

*p < 0.05 vs baseline by ANOVA, and vs time-matched control by unpaired t-test; #p < 0.05 vs baseline by ANOVA; X = mean + SE

EVLW was increased while ECFV remained unchanged, indicating that interstitial fluid accumulation was localized to the lung. Elevations in EVLW were independent of PCWP, implying differential responsivity of pulmonary and peripheral capillary beds to gram-negative sepsis.

117 EVIDENCE FOR HEPATOCELLULAR DYSFUNCTION DURING SEPSIS. J.G. Hauptman, G.K. DeJong*, K.A Blasko*, I.H.Chaudry. Michigan State University, East Lansing, MI 48824.

Although sepsis is frequently associated with organ failure, controversy exists as to whether there is hepatocellular dysfunction during sepsis. To resolve this, 27 male S-D rats (250-354 gms) were divided into two groups: 1) sepsis (CLP; two punctures; 18 gauge needle; n=16), and 2) sham (n=11). At 12-30 (mean = 19.2) hrs after CLP, the rats were anesthetized and two doses (D) of ICG (0.29±0.01 and 2.70±0.14 mg/kg; X±SEM) were given via a jugular catheter. [ICG] was continuously measured by a 2.4 F fiberoptic catheter inserted to the level of the aortic arch, and an in vivo hemoreflectometer (IVH); a technique that does not require blood sampling. The initial velocity of clearance (V_0) for each D was calculated from the progress curve of [ICG] vs time (t) according to the equation $[ICG]=a+bt+ct^2$, where a is [ICG] at t=0, and b is V_0 in mg/L/min. This V_0 was converted to mg/kg/min by V_0=bxBV/body weight and BV=mg ICG given/$[ICG]_0$. Hepatocellular function (maximal velocity of clearance of ICG; Vmax) was determined according to the Lineweaver-Burk transformation for Michaelis-Menten kinetics. The slow phase of excretion of ICG (k_2; representing biliary excretion) was the slope of the ln[ICG] vs time curve from t=29.2±0.6 to 46.3±1.1 minutes and reported as per min. The Vmax was depressed during sepsis (0.71 09 vs 1.51±0.35; P=0.0495). There was no difference in the slow phase (k_2) of Iu elimination (0.021±0.002 vs 0.025±0.004; P=0.42), suggesting that biliary excretion was unchanged. These results clearly demonstrate that hepatocellular function is depressed during sepsis. (Supported by NIH GM 39519).

118 RENOVASCULAR HYPERTENSION ALTERS SKELETAL MUSCLE MICROCIRCULATORY RESPONSES TO COMPLEMENT ACTIVATION BY AN ENDOTHELIUM-DEPENDENT MECHANISM. A.S. Lübbe, R.N. Garrison, P.D. Harris. Dept of Medicine, Virchow Medical School, D-1000 Berlin 19, FRG, and Depts of Surgery & Physiology, University of Louisville, KY 40292, USA.

1K1C-hypertension alters microcirculatory responses to E. coli sepsis. Skeletal muscle small arteriolar dilation in complement-activated normotensive (NT) rats is mediated by an endothelium-derived relaxing factor (EDRF). To test if 1K1C-hypertension blunts this response, we infused zymosan (5 mg/kg) 8 min i.v. into 1K1C-hypertensive (HT) pentobarbital-anesthetized (45 mg/kg) Sprague-Dawley rats (171±2g). Blood pressure (BP), thermodilution cardiac output (CO), and diameters of large (A_1) and small (A_4) cremaster muscle arterioles were measured via closed-circuit video microscopy. Then, maximal dilation of A_4-arterioles was induced by nitroprusside (NPR, 10^{-5} M). Results expressed as % change (± SEM) from baseline (BL) at 30 and 60 min after zymosan and after NPR were (*p<.05 for hypertensives vs normotensives):

	Normotensives (n=7)				Hypertensives (n=6)			
	BL	30 min	60 min	NPR	BL	30 min	60 min	NPR
BP	100±6mmHg	98±4%	98±4%	100±8%	151±3mmHg	100±1%	101±1%	92±6%
CO	94±6ml/min	105±5%	108±4%	105±2%	97±5ml/min	120±5%	125±6%	116±6%
A_1	112±8µm	91±2%	88±3%	95±2%	81±5µm*	104±2%*	102±1%*	104±1%
A_4	10±1µm	153±14%	178±21%	211±18%	10±1µm	98±4%*	102±4%*	170±13%*

In 1K1C-HT rats, large arterioles did not constrict after complement activation (c.a.) and small arterioles did not dilate. However, A_3 and A_4 did dilate with NPR, a postreceptor-acting agent. Therefore 1K1C-HT could blunt EDRF-mediated skeletal muscle small arteriolar dilation in complement-activated rats.

119 **EFFECT OF ENDOTOXIN (LPS) ON LABELED ARACHIDONATE (AA) INCORPORATION INTO HEPATOCYTES (HC) AND KUPFFER CELL(KC) PHOSPHOLIPIDS (PL).**
T. Lysz, T. Billiar*, R. Curran*, R. Simmons*, and G. Machiedo, N.J. Med. Sch., Newark, NJ 07103 and Univ. of Pitt., Pitt. Pa, 15261

Elevated LPS-KC prostaglandin E2 synthesis (measured by RIA) is increased further by HC addition to the culture. (J. Leuk. Biol. 43 (1987) 387). However, no 1-14C-PGs were measured in co-cultures after 1-14C-AA (3.6 uM) preincubation (determined by HPLC). To examine whether the lack of labeled PGs recovered was due to an altered uptake and release of AA into PL, rat HC and KC or their co-culture were incubated for 24 hrs with 1-14C-AA. After another 24 hrs +/- 10 ug/ml LPS, the labeled PLs were isolated by TLC. LPS had no effect on AA incorporation into HC. AA in KC phosphatidyl(P) serine/ inositol, ethanolamine (PE), and choline (PC) increased while neutral lipids (NL-AA) decreased ($P<.05$;$N=3$). LPS had no effect on total AA incorporated into the HC-KC co-culture PL but there was a marked change in the % distribution of AA between PE and PC (decreased) and NL (increased:$P<.01$;$N=3$). These results suggest that AA utilization in co-culture after LPS differs markedly from either the HC or KC and that the % AA incorporation into KC PL is modified by the presence of HC.

120 **INCREASED EXTRAVASCULAR LUNG WATER AND PULMONARY CAPILLARY PERMEABILITY ASSOCIATED WITH RAPID DEXTRAN INFUSION.**
R.C. Mackersie, F.R. Lewis*, Janet M. Christensen Univ. of Calif. San Francisco

Dextran solutions have been used in the resuscitation of burn and trauma patients, but their effect on lung fluid balance and interstitial edema has not been completely determined. To determine the effect of dextran on pulmonary edema and lymph composition under hydrostatic conditions, 14 sheep were prepared with a lung lymph fistula, and given a rapid IV infusion of either 10% Dextran 70 in saline, or homologous plasma, titrating pulmonary wedge pressure to 25 mm. Hg. for 10 minutes. Serial measurements of pulmonary lymph flow (Ql), paired plasma and lymph protein concentration ratios (L/P), pulmonary vascular pressures, and extravascular lung water (EVLW) were made.

	Plasma (n=6)	Dextran (n=8)
Baseline EVLW cc/Kg	11.1 ± 1.8	10.0 ± 1.4
Maximum EVL cc/Kg	14.7 ± 3.1	16.6 ± 6.3
EVLW unresolved (3 hrs)	.25 ± .5*	3.7 ± 5.9
L/P baseline	.63 ± .05	.66 ± .07
L/P (3 hrs)	.62 ± .07*	.87 ± .06

* $p < 0.05$, Wilcoxon rank sum.

L/P ratios and lymph protein clearance were higher in the dextran animals, and there was less complete EVLW resolution in the dextran group. These findings suggest that dextrans may produce an increased lung capillary permeability to protein, and may act to impair the normal resolution process of pulmonary edema.

121 **ADRENERGIC REGULATION OF HEPATIC BLOOD FLOW DURING ENDOTOXIN SHOCK**
M.P. McLane, M. Pyka, W.R. Law, and R.M. Raymond. Depts. of Surgery and Physiology, Loyola University Medical Center. Maywood, IL 60153 and the V.A. Hospital, Hines IL 60141.

Alterations in hepatic glucose output contribute to endotoxin-induced glucose dyshomeostasis. Hepatic metabolism may be affected by hepatic blood flow. To investigate the role of adrenergic regulation in response to ETX, hepatic blood flows were studied in response to ETX in the presence or absence of catecholamine blockade (CA-blk.) After an overnight fast, healthy mongrel dogs were anaesthetized with

sodium pentobarbital (30 mg/kg), intubated and ventilated on room air. Catheters were placed in a femoral artery and vein for arterial blood pressure (BP; mmHg) measurements and i.v. infusion of CA-blk: phentolamine (95 μg/kg bolus + 9.5 μg/kg-min infusion) and propranolol (70 μg/kg bolus + 5 μg/kg-min infusion). Hepatic arterial and portal vein blood flows (Q; ml/min) were measured using electromagnetic flow probes and total hepatic blood flow was the summation of these two flows. A one hour period for stabilization followed surgery. In CA-blk dogs (n=4) a basal period was followed by a 30 min infusion of CA-blk. Then while maintaining the CA-blk, ETX (1 mg/kg *S.enteriditis*) was administered i.v. bolus. In CONTROL dogs (n=5), a basal period was followed by ETX administration. Measurements were obtained during basal period, CA-blk period and during ETX. The CA-blk dogs died between 65 and 110 min post-ETX.

Group		MIN post-ETX 0	30	60	90	120	150
CA-blk	Flow	414±65	301±88	147±47	121±66	-	-
	BP	113±13	54±9	34±4	35±9	-	-
CONTROL	Flow	646±95	470±132	425±73	481±139	319±93	451±21
	BP	141±6	85±13	64±7	78±18	73±15	83±5

These data suggest that adrenergic regulation is involved in hepatic blood flow response to endotoxin shock. The involvement of the adrenergic regulation of ETX-altered hepatic blood flow in relation to adrenergic regulation of hepatic glucose output during ETX remains to be elucidated. (Supported in part by NIH grant #31163 and the VA).

122 ENDOTOXIN ADMINISTRATION STIMULATES IN VIVO GLUCOSE UTILIZATION BY KUPFFER CELLS Károly Mészáros*, Julia Bojta*, Charles H. Lang and John J. Spitzer. Department of Physiology, Louisiana State University Medical Center, New Orleans, LA 70112.

In vivo glucose utilization of macrophage-rich tissues, including the liver, increases after endotoxin administration. To investigate the contribution of the different cell types of the liver to this increase, conscious rats (fasted for 24h) were injected IV with endotoxin (100 μg/100 g BW) or saline. Three hours later tracer doses of ^{14}C-deoxyglucose (dGlc) and ^{3}H-galactosamine (GalN) were injected. After a 40 min in vivo labeling period, a small lobe was removed from the liver, and the rest of the organ was perfused and dispersed with collagenase. From the resulting cell suspension parenchymal cells were isolated by differential centrifugation, then endothelial and Kupffer cells were separated by elutriation. Intracellular metabolites of GalN were detected in whole liver tissue and in parenchymal cells only; their accumulation was not increased by endotoxin. The concentration of phosphorylated metabolites of dGlc increased about 3-fold after endotoxin administration in whole liver and in Kupffer cells, but not in parenchymal and endothelial cells. From the ratios of the intracellular metabolites of dGlc and GalN in whole liver and in parenchymal cells we calculated that non-parenchymal liver cells are responsible for at least 75% and 90% of glucose uptake by the liver of control and endotoxic rats, respectively. Thus, Kupffer cells are responsible for the elevated hepatic glucose utilization after endotoxin. (Supported by NIH GM 32654.)

123 CORE-SPECIFIC RECEPTOR FOR LIPOPOLYSACCHARIDE ON HEPATOCYTES. James B. Parent* (Spon: D.S. Malcolm), Metabolic Research Division, Naval Medical Research Institute, Bethesda, MD 20814-5055.

The liver is the major organ mediating clearance of LPS from the bloodstream. To determine if hepatocytes have receptors for LPS we have studied the binding of R-form LPS isolated from Salmonella rough mutants deficient in the biosynthesis of their complete (smooth) LPS polysaccharide. LPS was extensively purified and labeled with ^{125}I to 5 uCi/ug using Wood's reagent. Six of the R-form LPS tested (Ra, Rb1, Rb2, Rb3, Rc and Rd2) but not Re bind to rat hepatocytes via a specific LPS receptor since binding is: (1) competable with excess homologous or heterologous unlabeled LPS, (2) saturable (max binding 30-80 ng LPS/3,000 cells), (3) high affinity (1/2 max binding at 1-2 ug LPS/ml), and (4) inhibited by prior mild trypsinization of intact hepatocytes. In addition, all eight E. coli and Salmonella wild-type (S-form) LPS tested bind to hepatocytes via specific LPS receptors. These results suggest that high affinity binding requires LPS maturation beyond the incomplete core found in LPS isolated from Re mutants. Since the LPS hepatocyte receptor may be a lectin we tested the activity of various sugars as competitive inhibitors of LPS binding. We found that of the sugars tested only heptose (L-glycero-D-manno heptose), a unique component of the LPS core, is a potent inhibitor of LPS binding (50% inhibition at 1-2 mM). In preliminary experiments to characterize the hepatocyte LPS receptor we used a photoactivatable radioiodinated LPS probe (^{125}I-ASD-LPS) and SDS-

PAGE analysis and identified a 47 KDa integral membrane protein that appears to be subunit of the LPS receptor. We conclude that hepatocytes have high affinity LPS receptors which recognize the LPS core oligosaccharide (heptose region).

124 EFFECTS OF ENDOTOXIN ON RENAL FUNCTION AND TUBULAR ENZYME ACTIVITY. P.S. Rao, D.M. Cavanagh*, and E. Spaziani*. Dept. of Obstetrics & Gynecology, Univ. of South Florida College of Medicine, Tampa, FL 33612

This study was designed to evaluate the effects of intravenous infusion of endotoxin (0.25mg/kg) over a 4-hour period on renal function and tubular enzyme activity. Another group of dogs received isotonic saline and served as controls. The results of our study indicate that although the renal blood flow and urinary output are generally well maintained with the low dose infusion of endotoxin used in these experiments, creatinine clearance and osmolar clearance are decreased, suggestive of compromised renal function. The enzyme activities of alkaline phosphatase (ALP) and lactic dehydrogenase (LDH) did not change significantly in the serum, but were elevated in the urine as a reflection of renal tubular involvement. The increase in the urinary level of LDH (234%) was more pronounced than that of ALP (169%). In the saline control group such changes were not observed. These data suggest that an increase in urinary enzyme activity reflects compromised renal function and is independent of the renal artery flow. This observation may have significant practical application not only in endotoxemia, but also in the detection of early renal damage due to drug toxicity. Supported by BRSG SO7RR05749 and John R. McCain Student Fellowship Award of the South Atlantic Association of Obstetricians and Gynecologists.

125 MIGRATION OF 14C OLEIC ACID LABELED E.COLI TO THE LUNGS DURING HEMORRHAGIC SHOCK(HS) IN RATS. J.Redan*,B.Rush*,G.Machiedo,T.Lysz,and T.Murphy*.UMDNJ-NJ Med. School, Newark, NJ 07103

This study demomstrates that bacteria which move from the gut to the bloodstream of rats during HS are mostly trapped in the lungs in preference to other organs. Sprague-Dawley rats were fed 1 million counts of 14C oleic acid labeled E.Coli (specific activity of 1 count per 20,000 bacteria) by gavage followed 24 hours later with femoral artery cannulation. 24 hours post-cannulation 8 animals were bled to a mean systemic arterial pressure of 30 torr. The animals were maintained until either 80% of their maximal shed blood was returned or 5 hours of shock time had elapsed. At the end of shock all the blood was returned to the animal. Control(C) animals were gavaged, cannulated, but not shocked. After all the blood was returned, the heart, lung, liver, spleen, kidney, and serum were harvested and prepared for counting. The results are expressed as mean disintegrations ± SEM per gram of tissue and displayed below:

	N	HEART	LUNG*	LIVER*	SPLEEN*	KIDNEY*	SERUM *
HS	8	286±113	3708±845	283±47	106±4.3	170±20	947±85.5
C	5	40±20	68±24	68±9.9	56±4.9	70±20.6	50±6.7

*p<.01 by Student-Newman-Keuls "t" test

Based on specific activity there were 75 million bacteria per gram of lung. We conclude that during HS there is a prompt migration of the gut flora directly into the bloodstream and these were principally filtered out in the lungs of rats.

126 INOSITOL LIPID METABOLISM IN KUPFFER CELLS OF CONTINUOUSLY ENDOTOXEMIC RATS. J.A. Spitzer and E.B. Rodriguez de Turco, Louisiana State University Medical Center, New Orleans, LA 70112.

Kupffer (K) cells were isolated by elutriation from livers of rats that had been continuously infused with a non-lethal dose of E. coli endotoxin (LPS) for 30h via implanted osmotic pumps. Basal lipid metabolism in these cells was very active. The incorporation of ^{32}P into phospholipids (PLs) and ^{3}H-inositol into inositol lipids was 3- and 2.7 times higher than in cells from saline-infused rats. The % distribution of ^{32}P-labeling in LPS and saline cells showed lower labeling of phosphatidyl-

inositol (PI), 13.6% vs 16.5%), higher labeling of phosphatidylinositol 4-phosphate (PIP, 7.3% vs 4.1%) and similar % values for phosphatidic acid (PA) and phosphatidylinositol 4,5-bisphosphate (PIP_2) labeling. A similar pattern of changes was observed with ^{3}H-inositol as precursor, i.e. lower % labeling of PI concomitantly with higher labeling of PIP in LPS cells. Changes induced by LPS-infusion in K cells were in the same direction as we have previously reported for hepatocytes (Metabolism 36:753, 1987), including a shift of ^{32}P-PE (phosphatidylethanolamine) to ^{32}P-PC (phosphatidylcholine) labeling. This was reflected in a PC/PE ratio of 0.9 in saline-cells vs 2.7 in LPS cells. Challenge of the K cells in vitro with LPS (1 and 10 ug/ml) did not stimulate PA-PI turnover, but resulted in a 21% reduction of PI labeling, only in LPS cells and a 20% decrease in PC labeling in both conditions. The results are consistent with the idea that continuous endotoxemia leads in K cells to activated metabolism of PLs and inositol lipids associated with signal transduction mechanisms. (Supported by NIH grants GM32654 and GM30312).

127 ALTERATIONS IN DNA TOPOISOMERASE II AND O^6-METHYLGUANINE ACCEPTOR PROTEIN LEVELS IN SEPTIC RAT LIVER. K. S. SRIVENUGOPAL*, W. SCHUMER. University of Health Sciences/ The Chicago Medical School, North Chicago, IL 60064.

The involvement of gene expression and the changes in transcriptional/posttranscriptional mechanisms of gene regulation as a molecular basis for the myriad of biochemical changes and alterations of metabolic pathways that occur in septic shock, have not been investigated. In our preliminary studies to understand the molecular mechanisms of sepsis, we have quantitated in liver cells, the activities of two important enzymes related to DNA metabolism in a rat peritonitis model. These are: (a) DNA topoisomerase II (topo II), a nuclear non-histone protein that controls the DNA conformation and thus affects DNA functions in a global fashion--assayed by decatanation of (^{3}H)-kinetoplast DNA; and (b) O^6-methylguanine acceptor protein (MGAP), capable of removing the methyl groups from O^6-position of guanine in DNA, which otherwise are mutagenic--assayed by transfer of (^{3}H) methyl groups in DNA to MGAP. The specific activities (units/mg protein) of both topo II and MGAP were elevated by 1.4-fold and 1.6-fold, respectively in septic rat livers, compared to sham-operated controls. MGAP functions as a cellular stress protein (von Hofe E, Kennedy AR. In vitro induction of O^6-methylguanine-DNA methyltransferase in C3H/10T1/2 cells by X-rays is inhibited by nitrogen. Carcinogenesis 9:679-681, 1988.), and increased level of topo II is known to modulate altered gene expression. We conclude that similar alterations in DNA metabolism occur in the peritonitis septic model.

128 COMPARISON OF SEAWATER AND FRESHWATER NEAR DROWNING IN SHEEP. J. Stothert, G. Gbaanador, J. Basadre, L. Traber, D. Traber. Dept. of Surgery, University of Texas Medical Branch, Galveston, TX. 77550.

Pulmonary injury resulting from airway aspiration of seawater (S) or freshwater (F) has been studied over 48 hours in 8 chronically instrumented sheep. Each animal was anesthetized with 5mg/Kg of Ketamine during airway instillation of 11cc's/Kg of either freshwater or seawater. All animals were then monitored for 48 hours. The following parameters were then measured at the times listed below: cardiac index (CI), extravascular lung water (EW), pulmonary lymph flow (LQ), lymph to plasma protein ratio (L/P), and PaO2/FIO2 ratio (P/F). *p 0.03 from baseline by student t test.

	Baseline		0.5hrs		2.0hrs		24hrs		48hrs	
	S	F	S	F	S	F	S	F	S	F
CI L/min.	5.3	4.5	3.5*	3.3	5.0	2.8	5.3	3.7	4.8	4.4
EW mls.	450	326	1170*	475	1058*	610*	527	442	549	350
LQ ml/hr.	5.0	6.5	22*	23*	22*	12.3	9.5	12	9.9	10.6
L/P	.53	.58	.30*	.54	.33*	.65*	.50	.54	.47	.56
P:F	592	610	67*	401	213*	265*	333	590	407	580

These data suggest that at equal volumes of aspirated fluid, in a conscious animal, seawater results in more profound acute lung failure than freshwater. Immediate edema occurs with the seawater aspiration. Freshwater causes a pulmonary injury which is slower in onset, less severe, and probably associated with cellular hemolysis more than fluid flux changes.

129 EARLY HEMODYNAMIC AND VENTILATORY ALTERATIONS AFTER HYPERTONIC RESUSCITATION FROM HEMORRHAGIC SHOCK IN DOGS. R.C. Baenak, I.T. Velasco, M. Rocha e Silva, Heart Institute, Fac. de Medicina, Universidade de São Paulo, São Paulo, SP, Brasil

The immediate effects (0-2 min) of hypertonic NaCl administration in hemorrhagic shock upon cardiac output (CO), diastolic pressure (DP), mean arterial pressure (MAP), heart rate (HR), vascular resistance (VR), and respiratory rate (RR) have been examined in 33 pentobarbital anesthetized (25 mg/kg) dogs. Hypotension (MAP = 40 mmHg) was induced in 15 min and maintained by controlled hemorrhage and reinfusion. After 45 min of shock, dogs were randomized to receive IV NaCl infusions (0.9%, 3.75% or 7.5%) through a pump adjusted to deliver 50 ml in 78 sec. Pulmonary artery blood Na^+ and osmolarity were serially determined before, during and after infusions. Immediate variation of each parameter was dose dependent. Consequently, data from all the groups were pooled together for correlation analysis. Highly significant ($p < 0.001$) linear correlations were found between plasma osmolarity increase (OSM) and the maximal variation of Na^+ ($r=0.98$) and HR ($r=-0.76$). Equally significant exponential correlations were found between OSM and maximal alteration of MAP ($r=-0.82$), DP ($r=-0.84$), CO ($r=0.80$), VR ($r=-0.86$) and RR ($r=0.87$). These results are compatible with the concept of an early cardiopulmonary reflex triggered in dose dependent fashion by pulmonary artery osmolarity and consisting of bradycardia, hypotension, vasodilation and tachypnea.

Research supported by FAPESP, FINEP & FUNDAÇXO E. J. ZERBINI

130 COMBINED HEMORRHAGIC SHOCK AND HEAD INJURY: EFFECTS OF HYPERTONIC SALINE (7.5%) RESUSCITATION. F.Battistella*, D. Wisner. Univ. of Calif., Davis, CA., 95616

A large animal model was used to examine the effects of resuscitation in the setting of hemorrhagic shock with combined head injury. Sheep were subjected to a freeze injury of one cerebral hemisphere as well as two hours of hypotension at a mean arterial pressure (MAP) of 40 mmHg. Resuscitation was then carried out (MAP=80-90) for one hour with Ringer's lactate (LR,n=6), or 7.5% hypertonic saline (HS,n=6). Cardiac index (CI), MAP, intracranial pressure (ICP), serum osmolality (OSM), and urine output (UO) were followed. Brain water content was determined in injured and uninjured hemispheres after resuscitation. RESULTS (mean±SEM):

		BASELINE	SHOCK	RESUSC			BASELINE	SHOCK	RESUSC
MAP	LR	97±6	40±1	82±2	OSM	HS	292±3	294±2	290±3
(mmHg)	HS	100±6	41±1	77±8	(mosm/l)	HS	296±2	298±2	347±11*
CI	LR	3.4±0.2	1.5±0.2	4.4±0.8	ICP	LR	5.7±0.5	6.0±1.4	15.2±2.2
(l/min-m^2)	HS	3.7±0.5	1.6±0.2	3.9±0.5	(mmHg)	LR	7.7±1.2	10.0±1.7	4.2±1.5*
UO	LR	40±21	0.9±0.9	51±21					
(ml/30min)	HS	15±6	1.2±0.9	38±17					

* $p<0.005$ HS vs LR

Brain water content (ml H_2O/gm dry wt.) in uninjured hemispheres was lower after HS resuscitation (HS = 3.3±0.1, LR = 4.0±0.1, $p<0.005$).

CONCLUSIONS: Hypertonic saline abolishes increases in ICP seen in resuscitation of shock associated with head injury. This is due to a mannitol-like dehydration in areas where the blood-brain barrier is intact. Hypertonic saline may prove useful in the early management of the multiple trauma patient with head injury.

131 A DEVICE FOR RAPID VASCULAR ACCESS TO THE STERNAL MARROW SPACES FOR DELIVERY OF RESUSCITATION FLUIDS. Brian K. Bay*, Jerald M. Henderson*, F. William Blaisdell, George C. Kramer. University of California at Davis, Davis, CA 95616, and Departments of Mechanical Engineering, Human Physiology, and Surgery, and Letterman Army Institute of Research, San Francisco, CA 94129.

Intraosseous infusions of hypertonic saline/dextran have been used to successfully resuscitate hemorrhaged animals. In the present study, engineering design principles were applied to the problem of delivering low volume, concentrated saline/dextran solutions into red bone marrow for field treatment of hypovolemic shock. Special consideration was given to the field environment, the need for speed and safety, and the range of normal anatomic variation. This led to the development of a device that installs onto the midline of the manubrium or sternal body and delivers fluid into the marrow

circulation. Automatic adjustment for variations in tissue and bone thickness is incorporated into the device. Minimal training is necessary to properly use the device. An experienced technician can install the device and begin infusion in less than 30 seconds utilizing easily palpable landmarks. Design refinements have been based on prototype testing in human cadavers and anesthetized sheep. Entry rates of hypertonic saline/dextran into the circulation were identical for intraosseous and intravenous routes. All test results indicate that an intraosseous infusion device may provide paramedics with a means to gain rapid vascular access for fluid and drug delivery without the time delays and failures associated with field cannulation of peripheral vessels.

132 NON-LETHAL PORCINE INTRAABDOMINAL SEPSIS: CARDIOPULMONARY RESPONSE WITHOUT RESUSCITATION. K. Burchard, R. Damico*, A. Robinson*, H. Simms. R.I. Hospital/Brown University, Providence, R.I. 02903.

Twenty-four swine were subjected to femoral artery and pulmonary artery catheterization followed by sham laparotomy or cecal ligation and incision, resulting in three states of sepsis: no positive cultures, NS (3); line sepsis, LS (8); and intraabdominal sepsis (IS) with abscess and positive blood cultures for intestinal organisms (13). CI, arterial pO_2, PAP, MAP, PCWP, and BW were obtained on awake animals on days 0,1,2,4,7, followed by sacrifice to obtain cardiac blood and lung wet-dry weight. MAP was significantly lower on days 0 and 1 in IS compared to NS and LS, but CI was no different. PAP, PCWP, PVR, and wet-dry weight were no different. IS body weight (compared to day 0) fell, being significantly different from the increase in BW in NS and LS by day 4 (97% vs. 110% and 105%, $p < 0.05$, respectively). Arterial pO_2 fell in IS, significantly lower than NS and LS by day 4 (77 ± 3.2, 100 ± 4.3, 93 ± 4.6, $p < 0.05$, respectively). With this model, non-resuscitated porcine IS results in loss of weight and pulmonary dysfunction, which is not associated with increased lung water, major systemic, or pulmonary circulatory changes. We conclude that sepsis-induced pulmonary dysfunction is independent of the water sequestration and hemodynamic alterations most often recognized following sepsis resuscitation.

133 ALKALINIZATION THERAPY. G. Carroll. Rush Pres. St. Luke's MC, Chicago, IL 60612.

In human shock, decreases in blood pH from lactic acidosis have been treated with sodium bicarbonate ($NaHCO_3$). Such treatment has been criticized because the reaction of $NaHCO_3$ with acid ions (H) generates carbon dioxide (CO_2) (respiratory acidosis) which diffuses into cells where it forms H. Hypotension has been reported with $NaHCO_3$ administration in acidotic dogs; however, we have not seen HCO_3 induce hypotension in humans. Consequently, we studied a rat model of acute respiratory acidosis in which HCO_3 administration should hasten death. Methods: 60 anesthetized rats were hypoventilated with 1/6 their baseline minute ventilation until death. Each rat was assigned randomly to one of 5 groups of 12 rats each. Each were given 4 boluses of test agent. Group 1 received normal saline (NS) 1.5ml/kg; Group 2, 8.4% $NaHCO_3$ 1.5ml/kg; Group 3, hypertonic saline (HTS) (equi-osmolar to $NaHCO_3$) 1.5ml/kg; Group 4, Tham 5ml/kg (equi-alkalizing as $NaHCO_3$); and Group 5, large volume normal saline (LVNS) 5ml/kg. Results: $NaHCO_3$ and HTS boluses produced acute 3-phased or 4-phased disturbances in blood pressure with return to baseline in 2-3 minutes. Initially hypertensive, all animals died bradycardic and hypotensive. No hyperkalemic dysrhythmias occurred.

GROUPS	NS	$NaHCO_3$	HTS	THAM	LVNS	
*post Rx(H) neq/l	220	182	229	174	231	*significant
*post Rx(PCO_2)	225	265	230	224	220	
Death Time(min)	71	88	77	81	79	

Concl: $NaHCO_3$ and Tham lower blood H. Death is neither hastened nor delayed. Criticism of clinical use of $NaHCO_3$ in shock is not supported by this study.

134 FAILURE OF RED CELL TRANSFUSION ALONE TO IMPROVE OXYGEN CONSUMPTION IN HUMAN SEPTIC SHOCK. Steven A. Conrad, Kenneth A. Dietrich*, Cullen A. Hebert* and Michael D. Romero*. Louisiana State University Medical Center, Shreveport, LA 71130.

Supply dependency of oxygen consumption is well recognized in septic shock, and suggests covert tissue hypoxia. An increase in oxygen consumption ($\dot{V}O_2$) has been demonstrated in response to an increase in O_2 delivery ($\dot{D}O_2$) through improvement in cardiac output with or without an increase in hemoglobin (HGB). We examined the effect of red cell transfusion alone on oxygen delivery and utilization in human septic shock. Fourteen patients in septic shock who were hemodynamically monitored during blood transfusion were reviewed. Red cell tranfusion volumes of 615±62 ml were given over 3.9±0.6 hrs, during which other cardiopulmonary support was unchanged. The results are presented in the table:

	Units	Pretransfusion	Posttransfusion	Significance
Hemoglobin	(g/dl)	8.2±0.3	10.2±0.4	$p < .001$
Cardiac index	(L/min)	4.8±0.3	4.8±0.4	NS
Wedge pressure	(torr)	13.0±1.1	12.8±1.0	NS
$\dot{D}O_2$	(ml/min/M^2)	496±33	630±42	$p < .001$
$\dot{V}O_2$	(ml/min/M^2)	115±14	119±13	NS
Lactate	(mM/L)	5.6±1.4	5.0±1.4	NS

An increase in $\dot{D}O_2$ of 27% was observed, which resulted from an increase in O_2 content and not an increase in cardiac output. No significant change in O_2 utilization based on $\dot{V}O_2$ or lactate occurred. We conclude that O_2 consumption in sepsis is not benefited by improving $\dot{D}O_2$ via increasing O_2 content. This data suggests that supply dependency of $\dot{V}O_2$ is mediated primarily through an improvement in the flow component of oxygen delivery.

135 RAPID INFUSION SYSTEM FOR HYPOVOLEMIC TRAUMA PATIENTS M Dunham, R Lyles*, H Belzberg*, L Weireter, D Skurdal*, G Sullivan*, T Esposito* MIEMSS, Balt, MD 21201

In a randomized study, the Rapid Infusion System (RIS), which can infuse up to 1.5 L of fluid/min at 37°C, was evaluated in hypovolemic trauma patients against conventional fluid administration (CFA) techniques. The admission (adm) pH was 7.18 and 7.29 (p=.047) and adm systolic blood pressure was 54.7 and 82.2 (p=.012) for 16 RIS and 20 CFA patients. At 24 hours, the total fluids given were 20.0 and 23.6 L (p=.0000) and packed red blood cells 4.6 and 5.5 L (p=.002) for RIS and CFA despite no difference in hemorrhage. O_2 delivery / O_2 consumption (O_2 Del/Cons) was computed and post adm serum lactate levels were divided by the adm lactate (frac lac).

		Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6	Hour 10	Hour 24
Temperature	RIS	35.1	35.3	35.2	35.5	35.9*	36.4*	37.0*	37.8
	CFA	34.7	34.5	34.2	34.5	34.4	34.3	34.9	37.0
Frac Lac	RIS	0.97	0.92*	0.84*	0.84*	0.80	0.73*	0.56*	0.39
	CFA	1.03	1.26	1.20	1.24	1.15	1.16	0.97	0.50
02 Del/Cons	RIS	3.09	3.90	4.43	3.60	5.21*	4.13	4.00	4.26
	CFA	2.64	3.90	3.24	3.05	3.60	3.63	3.76	4.71
Ionized Ca++	RIS	3.00*	3.09	2.96	3.96*	3.60*	3.75*	3.52	3.78
	CFA	3.49	2.96	3.41	3.38	2.98	3.25	3.33	3.76
Mag++	RIS	1.36*	1.40*	1.47*	1.36*	1.33*	1.32*	1.37*	1.41
	CFA	1.19	1.03	1.11	1.04	1.04	1.04	0.94	1.22

(*p<0.05 between RIS and CFA)

The Rapid Infusion System is a useful device to preserve serum Ca^{++}/Mag^{++} and normothermia and restore tissue perfusion in hypovolemic trauma patients.

136 THE ROLE OF ANF IN THE DIURESIS FOLLOWING HYPERTONIC RESUSCITATION. T. P. English*, C.J. Weber*, J.W. Holcroft, R.A. Gunther, and G.C. Kramer. Depts of Surgery and Human Physiology, University of California, Davis, CA 95616.

Resuscitation of hemorrhagic hypovolemia with 7.5% NaCl/6% dextran 70 (HSD) is associated with a robust diuresis. We hypothesized that the diuresis was due to release of atrial natriuretic factor (ANF). In the present study we measured ANF by RIA in 5 euvolemic and 5 hemorrhaged sheep before and after infusion of 200 ml HSD. Mean results (±SEM) for arterial pressure (AP), mm Hg; left atrial pressure (LAP), mm Hg; urine output (UO), ml/30min; and ANF, pg/ml, are shown before and at 15 and 30 minutes post infusion.

Euvolemia	AP	LAP	UO	ANF	Hem.	AP	LAP	UO	ANF
baseline	99±5	1±3	33±10	46±13		101±6	2±3	46±8	39±17
hemor.	- - -	-	- - -	- - -		51±2	-2±3	10±2	45±12
15 min	108±6	5±2	146±45	194±87		101±2	1±3	68±17	45±11
30 min	104±5	4±2	140±44	121±38		99±2	1±3	85±34	43±11

A diuresis occurred after HSD infusion in both euvolemic and hemorrhaged sheep. Plasma ANF was increased only in the euvolemic sheep. We conclude that the diuresis following HSD resuscitation is not primarily modulated by ANF. Increased ANF release may require atrial stretch and pressures above baseline levels.

137 EFFECTS OF RESUSCITATION ON ACUTE GASTRIC MUCOSAL INJURY. K. Ephgrave, R. Kleiman-Wexler*, & K. Broadhurst*. Univ. of Iowa Colleges of Medicine & Pharmacy, and the Veterans Administration Medical Center, Iowa City, IA 52242.

Gastric mucosal injury after hemorrhagic shock may comprise both ischemic and re-perfusion insults. We compared the gross and microscopic gastric mucosal damage present in dogs 2 hours after full resuscitation from 2 hours of hemorrhagic shock (n=6) with the injury present in dogs sacrificed immediately after shock and return of shed blood (n=6). The purposes of the study were to determine the magnitude of reperfusion injury in this model, and to determine which hemodynamic or metabolic factors were associated with mucosal injury. Gross gastric mucosal injury was measured by planimetry, and microscopic damage was measured with an ocular micrometer. Hemodynamic (MAP,LVP,CI,PAP) and metabolic (pH, pO_2, Hct) parameters were similar in the two groups before and during shock. Reperfusion was not harmful to the ischemic gastric mucosa, as gross injury totalled 18.3±5.6% vs. 8.6±2.7% and microscopic injury 42.2±5.7% vs. 15.6±11.1%, respectively, in immediately sacrificed versus resuscitated dogs. Such rapid gastric mucosal restitution has previously been reported in models using necrotizing agents, but not from in vivo hemorrhagic shock. We found that the extent of mucosal restitution correlated strongly with LVP (r=.97), CI (r=.91), pH (r=.88) and MAP (r=.82) measured 2 hours after resuscitation. We conclude that gastric mucosal restitution rather than reperfusion injury dominates after resuscitation from hemorrhagic shock, and that the degree of restitution correlates with the success of resuscitation.

138 ENHANCED ENDOTOXIN EFFECTS ON MICROVASCULAR PERMEABILITY AND BLOOD URINE NITROGEN IN PLASMA FIBRONECTIN-DEFICIENT RATS. H.M. Jin, F.A. Blumenstock, T.M. Saba Shanghai Med. Univ., Shanghai, China & Albany Med. College, Albany, NY,12208

In rats immunoreactive plasma fibronectin (PFn) deficiency was induced by infusion of gelatin (gel, 12mg/kg) suspended in sterile 5% dextrose (dext,pH7.4)and the endotoxin (endo, 0111:B4,0.2mg/kg) was given intraperitoneally after gel. In controls 5% dext and 0.9% saline substituted for gel and endo. Then FITC-Dextran (FD,MW500,000,100mg/kg) was injected and FD concentration was measured as the degree of changes in microvascular permeability (MP). The rats were divided into 4 groups: gel plus saline (GS,n=5), gel plus endo (GE,n=6), dext plus endo (DE,n=6) and dext plus saline (DS,n=4). At 1 hr after infusion the level of PFn were declined about 75.34% and 73.42% in GS and GE respectively ($P<0.001$,vs 0 hr). As compared to DS there were decrease at 1 hr, 2hr ($P<0.01$) and 4 hr ($P<0.05$)in GS and GE. At 6 hr the content of PFn was returned. After administration of gel in vivo and vitro the results in crossed electrophoresis of plasma showed a formation of low immunoreactive Fn-gel complex. In Fn-deficient rats injected endo, we observed a greater decrease in FD at 1 hr (69.4%), 4 hr (75.8%) and in peritoneal lavage a marked increase at 6 hr (496.80%) in GE as compared to GS and DE ($P<0.05$,$P<0.01$). An increase (62.25%,$P<0.01$) of Blood Urine Nitrogen(BUN) was found at 6 hr in GE as compared to other or same groups between 1 hr and 6 hr. The results suggested there was an enhanced effects of endo on MP and BUN in Fn-deficient rats. This effects not only related to the decrease of PFn, but also to suppression of its immunoreactive opsonic activity.

139 **INTRAOSSEOUS INFUSION OF HYPERTONIC SALINE DEXTRAN: EFFECTS ON PULMONARY FUNCTION AND THE HISTOLOGY OF BONE MARROW.** G.C. Kramer, S.C. Mertens*, L. Halvorsen*, J.W. Holcroft, P.R. Perron*, R.A. Gunther. Departments of Human Physiology and Surgery, University of California, Davis 95616 and Letterman Army Institute of Research, San Francisco, CA 94129.

Intraosseous (IO) infusions have been proposed as a means for vascular access and delivery of hypertonic solutions for rapid resuscitation of hypovolemia. In previous studies, we demonstrated equivalent cadiovascular responses to resuscitation of hemorrhaged sheep with 7.5% NaCl/6% dextran 70 (HSD) infused either IO or IV. However, the usefulness of intraosseus resuscitation would be limited by significant bone marrow pathology or pulmonary embolism from marrow tissue. Ten awake sheep were subjected to 2hrs of hemorrhagic hypotension (arterial pressure = 50 mmHg, bled volume = 1.2-1.8 liters), and then resuscitated with a 200 ml IO infusion (2-4 min) of HSD. Cardiovascular function was normalized 1 min after infusion. No sheep showed any deleterious effect from the infusion on either blood gases or respiratory rate. All sheep survived in apparent good health until euthanasia after 1-2 d (n=5); 2 wks (n=2); or 6 wks (n=3). Histological examination of sternums showed that the bony trabeculae and marrow fat remained intact, but hemopoietic cells exhibited a focal washout in the vicinity of the infusion site at 1-2 d post infusion. Specimens from the injection sites after 2-6 wks show replacement of hypocellular areas with fiberous tissue. In all cases, these changes were confined to the injection sites and in no case were they greater than 0.6 cm in diameter. No functional or histological evidence for pulmonary embolism was found. These data suggest that intraosseous HSD resuscitation can be rapid, safe and effective.

140 'SCOOP AND RUN' OR RESUSCITATE UNCONTROLLED HEMORRHAGIC SHOCK WITH NORMAL SALINE OR HYPERTONIC SALINE. KRAUSZ MM, BAR ZIV M*, RABINOVICI R*, GROSS D, Hadassah University Hospital, Jerusalem, Israel, 91120.

The controversy of 'Scoop and run' (SAR) or resuscitate in hemorrhagic shock with normal saline (NS) or small-volume hypertonic saline (HTS) has not yet been setteled. Forty three rats were randomly assorted into three groops: gr 1 (n=13) uncontrolled hemorrhagic shock (UCHS) was induced by 12% resection of the terminal portion of the animals' tail and untreated (SAR). Gr 2 (n=13) UCHS was treated by 41.5 ml/Kg NaCl 0.9% (NS), gr 3 (n=17) UCHS treated by 5 ml/Kg NaCl 7.5% (HTS). Tail resection in gr 1 was followed by bleeding of 2.7±0.4 ml in 5 min and fall in mean arterial pressure (MAP) to 64±7 torr. A similar response was observed in gr 2 and gr 3. NS infusion was followed by further bleeding of 2.9±0.5 ml in 10 min, compared to 0.6±0.3 ml in the SAR gr ($p<0.001$). Infusion of HTS was followed by early bleeding of 1.9±0.2 ml in 10 min ($p<0.05$) with rise in MAP to 86±4 torr ($p<0.01$), and late bleeding of 1.0±0.3 ml with fall in MAP to 68±8 ml after 60 min, compared to 0.1±0.1 ml in gr 1 ($p<0.01$) and 0.1±0.1 in gr 2 ($p<0.01$). Total bleeding after 4 hours was 3.8±0.6 ml in gr 1, 6.7±1.1 ml in gr 2 ($p<0.01$) and 7.5±0.8 ml in gr 3 ($p<0.01$). It is concluded that large-volume N.S. treatment of UCHS leads to increased early bleeding from injured blood vessels while small volume HTS treatment leads to increased early and late bleeding. The least blood loss was observed in the untreated 'scoop and run' group.

141 CAPILLARY NARROWING IN HEMORRHAGIC SHOCK IS RECTIFIED BY INFUSION OF 7.5% NaCl/6% DEXTRAN 70. M. C. Mazzoni*, P. Borgström*, M. Intaglietta*, and K.-E. Arfors. Pharmacia Experimental Medicine - La Jolla, CA 92037 and AMES-Bioengineering, University of California, San Diego, R-012, La Jolla, CA 92093.

We have demonstrated previously that skeletal muscle capillaries narrow during hemorrhagic shock due to swelling of endothelial cells. The present study investigated the implications of fluid reinfusion in these narrowed capillaries. Intravital microscopy was used to visualize capillaries in the rabbit tenuissimus muscle during one hour of shock (40% hemorrhage) and subsequent reinfusion period initiated with a bolus infusion of either 7.5% NaCl/6% dextran 70 (HSD, dose equal to one-seventh of the shed blood volume) or Ringer's lactate (RL, dose equal to the shed blood volume). Changes in capillary lumenal diameter were inferred by changes in the width of red blood cells traversing the capillary. At the end of the shock period, the capillary diameter in the HSD (N = 7) and RL (N = 7) treatment groups was reduced by 23.9% and 21.6%, respectively. The resulting elevation in capillary hydraulic resistance may pose a mechanical hindrance to reflow. It appeared to be a contributing factor on RL infusion since only a transient increase in flow was observed, with no effect on the narrowed capillaries. In contrast, HSD infusion produced a sustained flow resurgence and a rapid reopening of the capillaries attributable to endothelium shrinkage with complete rectification of lumenal diameter in 30 minutes. We propose that HSD is a unique resuscitation fluid for hemorrhagic shock because it quickly restores systemic circulatory function, but also more importantly, it reinstates the microcirculation.

Supported by USPHS grants HL 12493, HL 17421, and HL 07089-14.

142 EFFECTS OF 30 % HYPERTONIC NACL ON THE BLOOD PRESSURE, CARDIAC OUTPUT, S. V. R., OSMOLARITY, ELECTROLYTES IN ENDOTOXIC DOGS. H. Ogata, K. Urabe. Department of Anaesthesia, Dokkyo University Schoolof Medicine, 880 Kitakobayashi, Mibu, Tochigi, 321-02, Japan

We applied 30 % NaCl to endotoxic shock using dogs and analyzed the blood pressure, cardiac output, S. V. R., osmolarity, electrolytes. Methods: Twelve dogs received 3 mg/kg of E. coli were served for the purpose to investigate the arterial blood pressure, central venous pressure, cardiac output (doppler transit time method), systemic vascular resistance, crystalloid osmolarity, electrolytes (Na+, Cl-, K+, Ca++). Two ml/kg of 30 % NaCl was injected each dog 3 hrs after administration of endotoxin and observed for further 3hrs. Results: Mean arterial blood pressure fell by 50 mmHg (about a 70 % decrease) in endotoxin alone, but hypertonic group indicated an increase of 30 mmHg in the mean blood pressure for 3 hours. Both systolic and diastolic blood pressure revealed a 40 % increase in hypertonic g. The cardiac output was increased by 125 % of pre-value after hypertonic solution and maintained 60 % of pre-value for 6 hours. But in endotoxin alone group C.O. was reduced by 27 % after 6 hours. Systemic vascular resistance was reduced transiently after hypertonic NaCl. Osmolarity indicated an increase of 50 mOsm/l compared with pre-value in both hypertonic and endotoxin group which means no statistic differences between both groups. Electrolytes indicated an increase of 35 mEq/l in both Na+ and Cl-, and a decrease of 2.5, 0.2 mEq/l in Ca++ and K+, respectively.

143 COMPARISON OF INTRACRANIAL PRESSURES IN AN EXPERIMENTAL MODEL OF HEMORRHAGIC SHOCK AND HEAD INJURY USING NORMAL SALINE, 3% SALINE,7.5% SALINE,DEXTRAN-70, AND DEXTRAN/SALINE COMBINATION FLUIDS FOR RESUSCITATION.J.Soyka*, J.Andrews*, W.Gunnar*, A.Robin*, M. Martin*, M.Moskal*, and J.Barrett.Cook County Hosp. and Univ. of IL. Sch. Med.,Dept.Surg.,Div. Trauma,Chicago, IL 60635

Using a splenectomized,closed head injury,hemorrhagic shock Beagle model, our research lab has shown that using 3% Saline for resuscitation of hemorrhagic shock induced by a rapid 40% blood shed is associated with a lower intracranial pressure(ICP) compared to normal saline(NS) and 10% dextran-40.This double blinded study compares the effects of NS, 3% saline(3NS), 7.5% saline(7.5NS), 10% dextran-70(D70), D70/3NS, and D70/7.5NS on ICP in this same model(n=5 for each fluid).All dogs received pentobarbital anesthesia as needed and controlled ventilation at a TV of 15ml/Kg and a FiO2 of 1.00.ICP was measured using a subarachnoid bolt and a simulated brain injury was induced by inflating a contralateral epidural balloon (BI) to 10mmHg above baseline (BL) ICP levels. After a one hour shock state (ES), each dog was resuscitated with blood equal to 1/2 the total blood shed followed by a test fluid volume equal to the amount of blood shed. ICP readings were continued for three 20 minute periods:early-resus(ER), mid-resus(MR),and late-resus(LR).The mean(±SD)ICP for BL,BI,and ES for all dogs was 7(±4)mmHg,17(±4)mmHg,and 9(±6)mmHg respectively. The BL, BI,and ES mean ICP values were not statistically significant (SS) between the six solution groups ($p<.05$).Mean ICP(mmHg) differences between BI and ER,MR,and LR, with all fluids compared to one another for SS,± SE are shown:

Deltas	NS	3NS	7.5NS	D70	D70/3NS	D70/7.5NS	3NS+7.5NS	D70/3NS+D70/7.5NS
BI	17±2	15±1	17±2	19±3	16±2	17±1	16±1	16±1
BI-ER	4±5b,d	12±1	16±3*	-5±6a,c,*	8±5	12±1	14±1b,c	10±2a,d
BI-MR	3±2b,d	11±1	18±2*	-9±7a,c,*	6±7	12±2	15±2b,c	9±4a,d
BI-IR	-.4±5b	10±1	19±2*	-9±7a,c,*	3±7	11±3	14±2b,c	7±4a

[a,b,c,d:$p<.05$ Wilcoxon(rank sum); *:$p<.05$ Scheffe's[for solutions in same delta]]

We conclude that hypertonic saline solutions(HTS),3NS+7.5NS,are equal to the D70/HTS combination fluids but superior to NS and D70 in maintaining a lower ICP during resuscitation of hemorrhagic shock in this head injury model.

144 INTRACEREBROVENTRICULAR (ICV) MORPHINE PREVENTS HYPERTONIC SALINE RESUSCITATION BUT ARGININE VASOPRESSINE INHIBITOR (AVPI) DOES NOT. I. T. Velasco, M. Rocha e Silva. Research Division. Heart Institute, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brasil.

A central neural component is involved in the survival response of hypertonic saline resuscitation, and we have demonstrated the critical involvement of central angiotensinergic pathways in the hemorrhage-hypertonic resuscitation interaction. Since it is known that endorphines inhibit central angiotensinergic conduction, and that some modes of AVP release are mediated by angiotensin, we examined the role of ICV morphine and AVPI in the hemorrhage-hypertonic saline resuscitation interaction. Severely bled (46±1 ml/kg) pentobarbital anesthetized dogs with chronically implanted cerebroventricular cannulae were resuscitated with 4 ml/kg NaCl 7.5% IV (HR), 10 min after ICV injections of 0.5 ml normal saline (CTRL), 10 ug morphine in 0.5 ml saline (MORPH), or 20 ug AVPI in 0.5 ml saline (AVPI). All 8 MORPH treated dogs died 2-8 hours after HR. Arterial pressure and cardiac index initially recovered to near prehemorrhage levels, but gradually decreased. Base excess shows progressive acidosis through shock and HR. All 8 CTRL and 8 AVPI treated dogs survived indefinitely with near normal arterial pressure, cardiac index and base excess levels. In conclusion, ICV morphine has the same effects of saralasin in preventing survival after HR, while ICV AVPI is ineffective.

Research supported by FAPESP, FINEP & FUNDAÇÃO E. J. ZERBINI

145 DEHYDRATION MODIFIES THE CARDIOVASCULAR RESPONSE TO HYPERTONIC SALINE DEXTRAN (HSD) RESUSCITATION C.E. Wade, F. Tillman*, A. Blackman*, E. Potanko*, J. Loveday* and M. Hunt*. LAIR, San Francisco, CA 94129.

The effect of dehydration on cardiovascular responses to HSD was evaluated in conscious swine (BW = 21 kg). Animals were euhydrate (E, n=5), or dehydrated for 24 (D24, n=7) or 48 hours (D48, n=6). Dehydration decreased body weight (0.9±0.5; -0.8±0.3; -1.7±0.1 kg) and increased plasma osmolality (Posm; 284±2; 303±5; 325±5 mOsm/kg). Animals were hemorrhaged 25 ml/kg/60 min and administered 4 ml/kg of HSD. Posm was increased by 11-25 mOsm/kg after HSD. HSD increased cardiac output (CO) in all groups but decreased over time. Mean arterial pressure (MAP) was increased but fell over time with dehydration. HSD restored cardiovascular function following hemorrhage in dehydrated animals but this improvement was transient.

			Min Post Resuscitation			
		Hemorrhage	5	15	30	60
CO	E	3.5±0.6	5.3±0.9	5.4±0.9	4.6±0.6	5.1±0.9
(l/min)	D24	3.3±0.4	5.9±0.8	5.2±0.3	4.1±0.2*	4.2±0.5*
	D48	3.2±0.5	6.4±1.0	6.0±0.7	5.2±0.4	4.7±0.7*
MAP	E	76±11	110±11	114±9	115±11	108±11
(mmHg)	D24	61±5	89±6+	72±9*+	75±7*+	75±8*+
	D48	74±8	120±9	99±6*+	80±6*+	85±9*+

P<0.05: * decreased from 5 min; + different from E

146 DETERMINANTS OF PERFUSION PRESSURE IN BRAIN INJURY AFTER SHOCK AND RESUSCITATION. J. Walsh*, S. Shackford, J. Davis*, J. Grimes*, Div.Trauma UCSD, San Diego, CA 92103

Autoregulation (AR) is thought to be lost after focal brain injury (FI). Determinants of cerebral blood flow (CBF) after FI and shock are unclear. We studied changes in blood pressure (BP), intracranial pressure (ICP), cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) after cryogenic FI, hemorrhagic shock (HEM) and resuscitation (RES),in swine. Group 1 had FI and increased BP induced by aortic clamping (XC) followed by declamping (DC) and RES. GRP 2 had FI and decreased BP induced by HEM followed by XC, RES & DC.

		BL	LESION	AOXC	AODC	
MAP (torr)	GRP 1	95±5	96±5	118±11*	77±4*	
	GRP 2	95±5	48±1*+	126±9*	78±4*	
ICP (torr)	GRP 1	8±1	15±3*	17±4*	18±5*	BL:baseline;
	GRP 2	10±2	10±1	17±2*	32±5*+	LESION:FI in GRP 1
CVP (torr)	GRP 1	13±1	14±1	14±1	16±2	FI+HEM in GRP 2
	GRP 2	7±1*	2±2*+	11±2	22±5*	*p<0.05 vs BL;
CO (l/min)	GRP 1	4.8±1.2	5.1±0.4	5.7±1.1	5.6±1.5	+p<0.05 vs GRP 1
	GRP 2	5.1±0.5	2.4±0.2*+	7.7±1.1*	7.5±0.9	
CPP (torr)	GRP 1	87±5	82±5	101±11	58±3*	
	GRP 2	84±5	38±1*	109±9*	45±3*+	

CBF fell with HEM in G2, was restored with XC, but decreased with DC. We conclude 1) AR is maintained after FI alone but is lost after FI & HEM shock;2) maintenance of adequate CO & MAP is insufficient to ensure adequate CBF & CPP after FI, HEM & RES.

147 EFFECT OF HYPOVOLEMIA AND TRANSFUSION ON TUMOR GROWTH IN MCA-TUMOR BEARING RATS. RN Younes*, A. Roqatko*, RG Bevilacqua*, S Meyer, N Vydelingum* and MF Brennan* (Spon: M. Rocha e Silva). Memorial Sloan-Kettering Cancer Center, New York, NY 10021.

Blood transfusions have been shown to induce immunosuppressive alterations and beneficial antirejection effects in renal transplant recipients. Evidence regarding the association of perioperative blood transfusions with recurrence of tumors is largely conflicting. To assess the influence of blood transfusions and hypovolemia as separate or combined factors, on tumor growth, we evaluated tumor weight (TW) in 35 rats. After reaching 1% tumor burden (day 0), they were separated into 2 groups: Hypovolemia (H-shed volume: 15 ml/kg) or Normovolemia (N). These groups were divided according to resuscitation: 00 (no resuscitation), BL (receiving syngeneic blood stored in CPD for 4 days), SL (receiving 0.9% NaCl). TW was determined daily. There was significant influence of hypovolemia on tumor growth, with no differences

related to resuscitation modalities (two-way analysis of variance, a=0.05). We conclude that the rate of growth of the tumor was not influenced by the resuscitation method, but was enhanced by the hypovolemic event in this experimental model.

TABLE: TUMOR WEIGHT (TW, g ± std dev)

Day	HOO	HBL	HSL	NOO	NBL	NSL
0	2.3±0.6	2.5±0.2	2.4±0.3	2.3±0.2	2.2±0.1	2.2±0.2
5	9.1±2.7	13.5±3.7	11.2±3.7	8.3±1.1	5.5±1.1	5.7±1.6
10	25.4±4.1	34.9±6.3	29.7±6.1	22.9±4.1	22.3±2.1	20.8±4.4
15	54.2±8.0	64.3±5.1	51.1±10.6	43.2±5.5	44.4±7.0	43.6±5.2
25	152.4±13.6	178.6±10.8	153.9±19.2	123.6±7.3	151.1±18.6	140.8±19.7

148 DILUTION OF RAPIDLY INFUSED HYPEROSMOLAR RESUSCITANTS AS MEASURED BY IN VIVO ELECTRICAL IMPEDANCE OF BLOOD. J.G.Alteveer* and R.J.Alteveer. Hahnemann University, Philadelphia, PA 19102.

Paramedics have reported cardiac arrhythmias after rapid infusion of 50 ml of 50% dextrose (D50) given to resuscitate comatose patients in the prehospital scene, a practice included routinely in state-approved paramedic protocols. The use of 7.5% NaCl (hypertonic saline, HS) infusions is likely to become common in response to recent impressive research reports. We designed electronic circuitry to monitor in vivo the electrical impedance of blood around 2 catheter-mounted electrodes. It gives a linear response to infusate dilution of blood (vol%): D50 (high impedance) or HS (low imp.). We rapidly (2-3 sec) infused 23 x 10 ml doses of D50 and 18 x 10 ml doses of HS into the R brachial or R axillary veins of 3 dogs (12.8-16.0 kg BW), and recorded dilution curves in the R ventricle (RV) and proximal aorta (AO). Maximal AO D50 concentrations reached 19±4 vol%, (530 mM = 9540 mg% glucose, 720 mOsm, Hct = 36%). Maximal AO HS concentrations reached 23±4 vol%, (400 mM NaCl, 827 mOsm, Hct = 33%). RV maxima were 28±4 vol% D50 and 31±5 vol% HS. Both infusates showed small recirculation curves. We recorded several cardiac arrhythmias and reduced pulse pressures during hyperosmolarity. We conclude that rapid infusion of hyperosmolar resuscitants risks diluting coronary blood. Since slower infusion may cause vascular wall damage, guidelines for their use should include recommended infusion rates, standards for which remain to be established. The electr. circuitry is also useful for in vivo measurement of CV volumes. Response is linear up to vessel radii of 45% of electrode distance, (d). At d = 1 cm, response is 0.3 V/mm.

149 EFFECT OF THYROTROPIN RELEASING HORMONE (TRH) IN THE ISOLATED RAT HEART K.C. Beamer, L. Teba, L. Shears II*, P. Quarantillo*, H. Dedhia*. Departments of Surgery and Anesthesiology and Medicine, West Virginia University, Morgantown, WV 26506

TRH exerts a positive inotropic effect in circulartory shock [1], but the mechanisms have not been elucidated. This study investigates the effect of TRH upon the isolated rat heart. Hearts of anesthestized adult rats were rapidly removed and connected to a Langendorff perfusion apparatus [2]. After 30 min equilibration, 14 hearts with cardiac output (CO) > 40 ml/min were studied for an additional 45 min. Seven hearts served as control (Ctrl), the remaining seven received TRH through the perfusate (10^{-4} mmol/L during the first 15 min and increased to 10^{-3} mmol/L during the remaining 30 min). CO and heart rate (HR) were measured. Data is reported as mean ± SD. Analysis of variance was employed to compare hemodynamic variables to baseline data. No significant differences for CO or HR were observed when TRH was added. Lack of intrinsic inotropic or chronotropic effect of TRH is seen in isolated rat hearts. This data indicates that the receptor for TRH is located outside the heart, and the positive inotropic effects seen in vivo are mediated through an indirect mechanism.

	CO ml/min		HR beats/min	
	TRH	Ctrl	TRH	Ctrl
baseline	54±10	56±6	241±24	212±16
15 min	54±10	54±10	242±18	212±28
30 min	53±12	52±13	242±18	212±31
45 min	50±13	49±13	241±21	212±31

References: Teba L, et al Circ Shock 1987, 21:51
Neely J R, et al Am J Physiol 1967, 212:804

150 SIMPLIFIED DIAGNOSIS OF METABOLIC ABNORMALITIES FROM BLOOD GASES IN SHOCK. Carlo Chiarla*, Ivo Giovannini, John H. Siegel, William P. Coleman*, Giuseppe Boldrini*, Marco Castagneto*. Centro Studio Fisiopatologia Shock, CNR, Catholic University, I-00168 Rome, Italy and Univ. of Maryland:MIEMSS, Baltimore, MD 21201

Data from 1936 blood gas measurements taken in 548 critically ill patients were extensively processed by regression analysis and other mathematical and statistical techniques in order to develop simplified formulae for the determination of arterial extracellular base excess (BE_{EC}, Severinghaus), the difference (ΔBE) between BE_{EC} and arterial base excess of the whole blood (BE_{WB}, Siggaard-Andersen), and CO_2 release from tissues into blood (CO_2 R). The following formulae were obtained:

A) $BE_{EC} = 0.58\ (PaCO_2 - 40) + 67.8\ (pHa - 7.4)$
n=1936 r^2=.97 F=33x10^3 p<0.001

B) $\Delta BE = 0.08\ (PaCO_2 - 40) - 2.41\ (pHa - 7.4)$

C) $CO_2R = 0.36\ (P\bar{v}CO_2) - 0.39\ (PaCO_2) + 0.33\ (a\text{-}\bar{v}O_2\ Diff) + 1.19$
n=1936 r^2=.97 F=24x10^3 p<0.001

Ranges: BE_{EC} = -19.61 to 30.78 mmol/L, BE_{WB} = -22.57 to 23.90 mmol/L, CO_2R = 0.59 to 11.9 ml/100ml, $PaCO_2$ (arterial CO_2 tension) = 19.2 to 88.0 mmHg, $P\bar{v}CO_2$ (central venous CO_2 tension) = 25.0 to 94.0 mmHg, pHa (arterial pH) = 6.99 to 7.64, $a\text{-}\bar{v}O_2$Diff (art.-central venous O_2 content diff.) = 0.39 to 10.5 ml/100ml, Hb (hemoglobin)= 5.2 to 18.4 g/dl. The very high r^2 in the comparison with measurements performed with standard procedure (Severinghaus, Siggaard-Andersen and others) and the good distribution of residuals indicate that these formulae represent an accurate and useful alternative to the more complex methods commonly used for determining BE and CO_2R.

151 ANTITHROMBIN III AS A PROGNOSTIC INDICATOR OF SURVIVAL IN 27 CASES OF EQUINE COLIC. B.J. Darien*, J. Potemp*, J.N. Moore, J. Travis*. University of Georgia, Athens, GA 30602

Antithrombin III (AT-III) determination is an important test for the diagnosis of disseminated intravascular coagulation (DIC) and for monitoring efficacy of therapy in patients with DIC (Semin Thromb Hemost 8:276, 1982). Abnormalities in coagulation parameters in clinical cases of colic suggest that the development of DIC as a complication of colic may be an important factor influencing the outcome. In light of this association, we evaluated AT-III activity as a prognostic indicator for survival in surgical cases of equine colic. Twenty-seven clinical cases of colic had blood drawn at the time of admission for AT-III activity and underwent exploratory laparotomy within six hours of hospitalization. AT-III activity (residual thrombin activity) was determined by chromogenic substrate assay (S-2238, Kabi) and expressed as a percentage of normal equine AT-III activity. Chi square analysis was used to compare survivors to non-survivors with respect to AT-III activity being greater or less than 60% of normal. Of the 27 horses, 13 lived and 14 died. AT-III activity of the surviving group (69.5% + 3.6 SEM) was significantly greater ($P<0.01$) than that of the non-surviving group (55.9% + 2.9 SEM). Sixty percent of normal AT-III activity appeared to best separate survivors and non-survivors. Surgical colics with AT-III activity >60% of normal prior to surgery were more likely to survive ($P<0.01$) than surgical colics with AT-III activity <60% of normal. This clinical trial suggests that AT-III activity may be used as a prognostic indicator for survival in surgical cases of equine colic.

152 LACK OF REGIONAL EFFECTS OF ACUTE ENDOTOXEMIA ON NA-CA EXCHANGE IN THE HEART. C.C. Hale*, J.A. Allert*, R.S. Keller*, H.R. Adams and J.L. Parker Dept. of Veterinary Biomedical Sciences and the Dalton Research Center, Univ. of Missouri-Columbia, Columbia, MO 65211

We tested the hypothesis that cardiodynamic changes during acute gram-negative endotoxemia could be associated with alterations in Na-Ca exchange across the myocardial sarcolemmal (SL) membrane in either the left or right ventricle. Pentobarbital-anesthetized dogs (n=4/group) were given either 1.5 mg/kg purified *E. coli* endotoxin (ET) or equivalent saline vehicle (C) by i.v. injection. Hemodynamic parameters were monitored for 2 hr to confirm endotoxemia-induced changes in shock dogs, after which hearts were removed for parallel isolation of SL vesicles from both the left and right ventricular free walls. Control hemodynamics remained constant

during the 2 hr *in vivo* period, while ET group mean arterial pressure decreased from 120 to 60 mmHg, heart rate increased from 130 to 190 BPM, and packed cell volume increased from 38 to 60%. Initial rates (2 sec) of Na-Ca exchange of left and right ventricle for C and ET were 3.44, 3.28, 3.13, and 3.01 nmol Ca^{2+}/mg protein respectively, which were not significantly different. The stoichiometry of Na-Ca exchange was measured by a previously reported method (JBC 259: 7733-7739, 1984). The stoichiometric relationship of the exchange of Na^+ for Ca^{2+} in left and right ventricle for C and ET were 2.74, 2.69, 2.84, and 2.72 respectively, which were not significantly different. We conclude that during the acute phase of endotoxemia, there were no endotoxin-mediated changes in cardiac Na-Ca exchange from either left or right ventricle and that the exchange process remained electrogenic with a stoichiometry of $3Na^+$ for $1Ca^{2+}$. (supported by NIH HL-36079, NSF DCB-86902234, and AHA - MO Affiliate)

153 HYDROXYETHYL STARCH DOES NOT ALTER PLASMA CLOTTING TIMES OR PLATELET AGGREGATION AT CLINICALLY RELEVANT CONCENTRATIONS

Thomas D. Johnston*, Ying Chen*, Judy Hudson*, Ronald P. Fischer, and R. Lawrence Reed, II. University of Texas Medical School at Houston, Houston, TX 77030

Anticoagulant properties have been attributed to hydroxyethyl starch (HES) plasma expanders, although little data is available to substantiate these claims. This study was undertaken to determine whether this was the result of dilution of clotting factors or true inhibition of clotting by HES. Normal human assayed reference plasma (ARP) was diluted with 6% HES in 0.9% saline or with 0.9% saline alone (SAL). Prothrombin times (PT) and partial thromboplastin times (PTT) were performed using an automated coagulation timer. Platelets were obtained from healthy donors and diluted in the same manner. Platelet aggregation profiles (PltAg) were obtained using 5 μM ADP as the aggregation stimulator.

%ARP	PT-SAL	PT-HES	PTT-SAL	PTT-HES	PltAg-SAL	PltAg-HES
100%	13.3±0.2	13.3±0.2	29.6±0.8	30.6±0.1	79.8±2.6	79.5±6.5
95%	13.4±0.1	13.5±0.1	28.3±0.1	29.0±0.1	77.7±3.6	84.7±0.7
90%	13.6±0.1	13.6±0.1	28.9±0.2	29.6±0.5	80.1±3.8	83.2±4.2
75%	14.5±0.1	14.7±0.2	30.5±0.1	31.4±0.4	89.2±1.2	79.5±2.2
50%	16.5±0.1	16.6±0.2	37.0±0.2	39.6±0.1	87.7±1.2	83.0±2.0
25%	23.3±0.2	25.1±0.8	54.7±1.3	67.6±0.7	88.5±6.0	80.2±3.25

Results are means±SEM of 6 determinations. No statistically significant differences exist between SAL and HES at any dilution for any test. However, significant prolongation of the PT and PTT is observed with progressive dilution in both groups. These data suggest that HES possesses no intrinsic anticoagulant activities. Whatever anticoagulant effects are ascribed to it may be the result of dilution alone, which occurs equally well with normal saline.

154 BIOELECTRIC IMPEDANCE ANALYSIS (BIA) AS A PREDICTOR OF SEPSIS AFTER TRAUMA. K. Kudsk, J. Glezer,* G. Voeller, and T. Fabian, University of Tennessee, Memphis, TN 38163.

The hormonal response to severe injury stimulates water retention which is excreted as the stress response resolves. Sepsis maintains the high stress hormone levels, preventing diuresis. Total body water (TBW) was measured daily using BIA (1) in 28 (4 Female/24 Male) severely injured (ISS = 26.2 ± 10.2; TS = 10.5 ± 2.0), potentially septic trauma patients to define its use in predicting subsequent sepsis. BIA estimates TBW by measuring the electrical resistance of the body. 11 patients sustained penetrating wounds, while 17 sustained blunt injury.

Results: 23 patients had no sepsis and had prompt decreases in TBW. None developed sepsis. TBW measurements were as follows:

Day	1	2	3	4	5	6	7	8	9	10
(liters)	49.1 ±8.3	49.3 ±7.6	47.8 ±7.0	45.9 ±5.6	44.6 ±5.9	43.9 ±6.8	42.5 ±6.7	43.2 ±6.1	42.2 ±7.0	42.4 ±6.9

4 patients developed systemic sepsis and increased TBW in 1 of 2 patients. 2 patients experienced initial diuresis but had subsequent increases in TBW several days before diagnosis and treatment of a pneumonia or intraabdominal abscess. 2 patients progressively increased TBW without initial diuresis. One died on day 5 of sepsis, renal and liver failure, while the other increased TBW until appropriate antibiotic therapy for pneumonia was instituted. A fifth patient with sepsis developed an abscess not associated with TBW increase as a lesser sac abscess drained continually through a flank bullet exit site post operatively.

Conclusion: Failure to diurese fluid post injury can be documented by serial BIA measurements and is predictive of an increased septic potential.

155 CARDIOVASCULAR CHANGES IN DIABETIC DOGS DURING ENDOTOXIN SHOCK W.R. Law, M.P. McLane*, and R.M. Raymond Depts. of Surgery and Physiology, Loyola University of Chicago, Stritch School of Medicine, Maywood, IL, 60153, and the V.A. Hospital, Hines, IL, 60141.

Cardiovascular impairments associated with diabetes mellitus may contribute to a sepsis-related mortality rate higher than that seen in non-diabetics. To test this, diabetes was induced in three mongrel dogs by the intravenous administration of 30mg/kg streptozotocin and 50mg/kg alloxan. Resultant blood glucose was >200mg/dl. After 30 days, dogs were anesthetized (50 mg/kg pentobarbital) and instrumented to obtain left ventricular (LV) pressure (Konigsberg transducer), LV minor axis diameter (sonomicrometry), aortic (CO) and coronary (Q) flow (electromagnetic probes), and mean arterial blood pressure (Statham; MAP), as previously described. The end-systolic pressure-dimension relationship was used to assess contractility (E_{es}), and LVdP/dt to index global LV performance. Arterial and coronary sinus O_2 contents were used to determine O_2 supply to demand ratios (S/D) and O_2 extraction (X). One hr post-surgery baseline values were obtained, then endotoxin administered iv (E. coli; 17μg/kg/min; Difco) for 1 hr. Measurements were made every 30 min after beginning endotoxin infusion. The mean values for MAP, CO, LVdP/dt, and Q during endotoxin shock in the diabetic group were lower than in the control (non-diabetic, endotoxic; n=3) dogs. Compared to pre-endotoxin, the mean E_{es} value (mmHg/mm) in the diabetic group had fallen from 20.4 ± 2.9 to 11.6 ± 2.4 at 2 hours post-endotoxin while control dogs went from 22.9 ± 2.9 to 23 ± 3.9. In diabetic dogs myocardial O_2 S/D decreased and O_2 X increased. The opposite response was seen in controls, where O_2 S/D increased and O_2 X decreased. These data suggest that cardiodynamic and coronary vascular changes in vivo may contribute to the increased sepsis-related mortality rate in diabetic subjects. (Supported by the American Diabetes Association, Northern Illinois Affiliate Young Investigator Award, and in part by NIH Grant HL-31163 and the V.A.)

156 THE ROLE OF ADENYLATE CYCLASE IN THE TRANSDUCTION OF PULSATILE STRETCH SIGNALS TO ENDOTHELIAL CELLS. G. Letsou*, I. Mills*+ and B.E. Sumpio. +Brown Univ., Providence, RI 02903 and Yale Univ. Sch. Med., New Haven, CT 06510.

The response of endothelial cells (EC) to hemodynamic alterations during shock may be important in mediating the shock state but the mechanisms are ill-defined. We have previously shown that pulsatile stretching of EC in culture will increase their rates of proliferation and regulate their secretion of macromolecules, such as prostacyclin. The aim of this study was to determine whether membrane adenylate cyclase (AC) is involved in intracellular signalling during pulsatile stress. EC from bovine aorta were seeded on flexible-bottomed culture wells (3 x 10^5 cells/25 mm well) and allowed to attach for 48 hours. The culture wells were placed in a vacuum-operated stress providing instrument and subjected to 0.5 s of 24% strain, 0.5 s relaxation (60 cycles/min) for 0, 1, 3, 5, 7, 10 and 15 minutes (n=24 wells/time point). Cell were homogenized in buffer containing 30 mM Tris (pH 7.5), 1 mM $MgCl_2$, 10 mM creatinine phosphate, 1 mM creatinine phosphokinase, and 1 mM DTT. A crude membrane preparation (27,000 x g) was assayed for AC under basal and forskolin (100 μM) stimulated conditions. Values for AC (pmoles/min/mg protein) are shown below. *$p<0.05$ compared to stationary control (0 min).

	Control	1 min	3 min	5 min	7 min	10 min	15 min
Basal	0.85	1.01*	1.14*	1.31*	2.15*	0.87	0.87
Forskolin	2.17	2.16	3.29*	3.69*	3.67*	2.99*	2.32

This time-dependent increase in AC with cyclic deformation suggest that there may be a stretch "receptor" coupled to AC which might modulate EC function with hemodynamic changes.

157 CHRONIC ALCOHOL CONSUMPTION ENHANCES THE CARDIAC DEPRESSION INDUCED BY SEPSIS. K.H. McDonough, Physiology, LSU Medical Center, New Orleans, LA 70112.

Chronic alcoholism causes a cardiomyopathy which, in rats, occurs after 6 mo. to a year of alcohol consumption. Sepsis, on a more acute basis, also induces cardiac dysfunction. In the present study we tested the hypothesis that 2 mo. of chronic alcohol feeding, while not directly causing overt depression of the myocardium, might sensitize the heart to a known cardiac stress, sepsis. We proposed that sepsis, induced in an alcoholic animal, would cause a more severe myocardial depression than in a nonalcoholic rat. Thus rats were fed a liquid diet with 36% of the total calories as alcohol for 8-9 weeks. Rats were then anesthetized and, after the placement of a dorsal subcutaneous catheter, received an injection of live Escherichia coli (10^9-10^{10} E coli/ml) followed by a second dose approximately 5 hr later. The following day, hearts were removed and, using the isolated working

heart preparation, ventricular function curves were generated. Four groups of animals were studied. Hearts from the nonalcoholic nonseptic group and the alcoholic nonseptic group showed identical cardiac work (cardiac output x peak systolic pressure at the highest preload was 6113 ± 324 and 5955 ± 406 ml/min x mmHg, respectively). Work in the nonalcoholic septic and the alcoholic septic groups was decreased by 30% and 50%, respectively (4806 ± 478 vs. 2917 ± 435 ml/min x mmHg at the highest preload). Thus, 2 mo. chronic alcohol consumption caused no overt cardiac dysfunction by itself but did potentiate the myocardial injury induced by sepsis.

158 CARDIOVASCULAR CHARACTERISTICS OF HYPOTHERMIC SHOCK. H.I. Miller and E. Giaimo, Physiology, Louisiana State University Medical Center, New Orleans, LA 70112.

Impaired cardiac and renal function, as well as metabolic changes are among the many abnormalities observed following prolonged exposure to very low ambient temperatures which lower body temperature and produce hypothermia. Upon rewarming, after prolonged low body temperature, there are symptoms of circulatory shock and many die. The question is whether the circulatory failure is due to peripheral or cardiac failure. A guinea pig model which utilizes indwelling arterial and venous catheters as well as an arterial thermistor bead was used to investigate the physiologic perturbations of severe hypothermia. In this model, guinea pigs were anesthetized with Ethrane and immersed in a water-ice mixture. Core temperature was monitored from the aortic thermistor and cardiac output was measured at various intervals. The animals were removed from the ice water bath when the body temperature reached 25°C, dried and rewarmed to their pre-immersion temperature. After the animal was completely rewarmed, and after 4 and 24 hours an overdose of sodium pentobarbital was given and the heart was excised and hung on a working heart apparatus. 50% of the animals died within 24 hrs after rewarming. Hearts excised during hypothermia showed no cardiac dysfunction, nor did hearts perfused just after rewarming. However, hearts perfused 4 hrs after rewarming had a depressed and flat Starling curve. This showed the hearts inability to increase work with increased demand. The mechanism of this change is not known at this time. The depressed cardiac function is similar to what is seen after endotoxic, septic and burn shock.

159 EVALUATION OF LIPOSOME ENCAPSULATED HEMOGLOBIN (LEH) AS ARTIFICIAL BLOOD IN THE CONSCIOUS RAT. R. Rabinovici*, A.S. Rudolph*[a], G. Feuerstein, USUHS, Bethesda MD 20814 and NRL[a], Washington, D.C. 20375.

One approach in the search for an O_2 carrying blood substitute is a synthetic erythrocytes solution composed of LEH. An LEH preparation characterized by an O_2 carrying capacity of 50% at 18 mmHg, and standardized by size at 0.5μ, was evaluated for its cardiovascular, hematological and biochemical effects in conscious rats (n=7). Under halothane anesthesia, catheters were introduced into the femoral artery and vein, tunneled subcutaneously and exteriorized at the posterior neck. The rats were allowed to recover for two hours. LEH, liposome vehicle (LIP) or 0.9% Nacl (NS) at doses of 1.4, 2.8 and 5.6 ml/kg were injected IV. Each rat had only one injection of a given dose of LEH, LIP or NS. Mean arterial pressure (MAP) and heart rate (HR) were monitored up to 180 min. Blood samples for Hb, WBC, Platelet count, TXB_2 (RIA) and 6-Keto-$PGF_{1\alpha}$ (RIA) were assayed. LEH increased MAP (max +19±5 mmHg, $P<0.01$) and HR (max +117±18 BPM, $P<0.05$). Platelet count dropped by 60% ($P<0.01$), while TXB_2 increased by +25±5.4 pg/100μl ($P<0.01$). The platelet and TXB_2 responses showed negative correlation ($R=-0.625$, $P<0.01$). There were also leukocytosis (lymphocytosis) and hemoconcentration. Unlike LEH, LIP decreased MAP (-16±5 mmHg, $P<0.01$), while all other responses were similar to LEH. All observed effects were transient and basal levels obtained at 120 minutes. These data show that LEH has distinct cardiovascular and hematological effects which might be mediated by TXA_2. Therefore, such LEH could be improved by incorporation of TXA_2 antagonist/synthesis inhibitor.

160 BIPHASIC EFFECTS OF ENDOTHELIN ON THE ISOLATED WORKING PERFUSED HEART AND 3'5' CAMP ACCUMULATION BY MYOCYTES. Raymond E. Shepherd, Alastair H. Burns, Howard G. Lippton*, Albert Hyman*, and Warren S. Summer*. Louisiana State University Medical Center and Tulane Medical Center, Departments of Physiology and Medicine, New Orleans, LA 70112.

The effects of rat endothelin (REDT) on cardiac performance in isolated working heart preparations and cAMP accumulation in myocytes and sarcolemmal membranes were investigated. At a constant preload of 7.5 cm water, a 10 minute perfusion with 0.04 and 0.4 nM REDT produced a positive inotropic effect. Prolonged exposure to low concentrations of REDT or exposure to higher levels (4-20 nM) resulted in a cardiac depression characterized by decreased coronary flow and increased myocardial oxygen extraction. This could be blocked by the protein kinase C inhibitor H-7. Myocytes and sarcolemmal membranes were used to determine the responsiveness to isoproterenol challenge in the presence of REDT. REDT did not alter the generation of cAMP in membranes but produced a biphasic effect in myocytes inhibiting at low concentrations (4 and 40 pmols). Taken together the data indicate that intact cells are necessary for REDT to produce its effect on cAMP accumulation and that REDT depresses cardiac performance through activation of protein kinase C. Supported by HL 38761 and GM 35390.

161 EARLY PHYSIOLOGIC PREDICTORS OF SHOCK AND THE RISK OF DEATH IN MULTIPLE TRAUMA. John H. Siegel, Avraham I. Rivkind*, Shirin Goodarzi* and Samir Dalal*. MIEMSS:University of Maryland and Department of Surgery, Baltimore, MD 21201.

The importance of admission physiological and biochemical parameters was modeled on data from 185 blunt liver trauma patients with regard to their significance in prediction of mortality. The parameters used were Glasgow Coma Score (GCS), Base Excess (or deficit) (BEA). Arterial lactate (LACT), Injury Severity Score (ISS) and initial 24 hour volume of blood (BL24) required for replacement. Each variable was modelled as a predictor of survival alone and in combination using a **linear logistic model.** The most important variables in descending order of significance as predictors of mortality were BL24, GCS, BEA, with lactate and ISS being much poorer. In any 2 variable combination, GGS had a high likelihood ratio for prediction, representing the influence of brain injury, but as a single variable reflecting the probability of death both BEA (LD_{50}=-11.8 mM/ℓ) and BL 24 (LD_{50}=5.4 ℓ) were highly significant (p<.0001) with BEA p<.05 for the likelihood ratio of prediction. Considering that BEA is available immediately, but BL24 requires 1 day of therapy for evaluation, a combined logistic model of admission GGS and BEA had the greatest early likelihood of accurate prediction of outcome:

$$P\ death = e^{\lambda}/1+e^{\lambda};\ where\ \lambda = -0.21(GCS)-0.147(BEA)+.285$$

This model not only predicts outcome, but is highly correlated with the subsequent need for blood volume in the initial 24 hour period. Testing of this predictive model on data from 324 additional multiple trauma patients who had pelvic fracture as their index injury also showed it to be a highly significant (p<.0001) early predictor of outcome.

162 A PROSPECTIVE COMPARISON OF CENTRAL VENOUS VS. MIXED VENOUS GASES IN POST-OPERATIVE CRITICALLY ILL GENERAL SURGICAL PATIENTS. H. Simms, D. Asprinio*, R. Meltzer*, K. Burchard. Dept. of Surgery, Rhode Island Hospital, Providence, RI 02903.

A prospective study was performed in 10 post-operative critically ill general surgery patients to determine the similarities (or lack of) between central venous oxygen pressure ($Cv0_2$), central venous oxygen saturation ($Cv0_2$ sat) and mixed venous oxygen pressure ($Sv0_2$) and mixed venous oxygen saturation ($Sv0_2$ sat). All patients had experienced a period of sepsis or septic shock secondary to intra-abdominal sepsis. There was no statisically significant difference between $Cv0_2$ and $Sv0_2$ or $Cv0_2$ sat or $Sv0_2$ sat. ($Cv0_2$, = 38.72 ± 6.68, $Sv0_2$ = 36.93 ± 3.68; p = ns; $Cv0_2$ sat = 67.66 ± 5.90, $Sv0_2$ sat = 69.03 ± 7.85; n = 28 p = ns). In addition, oxygen consumption ($V0_2$) measurements when calculated using either central venous or mixed venous gases were

not statistically different and were highly correlated. ($V0_2CVG$=278.06 ± 68.09; $V0_2SVG$ = 263.56 ± 69.09, p = ns; $V0_2CVG$ vs. $V0_2SVG$ r= .0857, P 0.001). As opposed to a separate group of hemodynamically stable post-cardiac surgical patients, neither cardiac output nor the ratio of $DO_2/V0_2$ correlated with either $Cv0_2$ sat or $Sv0_2$ sat. Monitoring of central venous blood gases, particularly with reference to oxygen pressure and oxygen saturation, may be a useful substitute for mixed venous gas measurements in many critically ill patients, thereby mitigating the need for pulmonary artery catheterization.

163 EFFECT OF A SELECTIVE V_1 VASOPRESSIN RECEPTOR ANTAGONIST ON THE SEQUELAE OF ENDOTOXEMIA IN THE CONSCIOUS RAT. E.F. Smith III, J.W. Egan*, M. Jugus*, L.B. Kinter* and K. Lee*. Smith Kline and French Labs, King of Prussia, PA 19406.

It is well established that the administration of endotoxin is associated with an elevation in plasma arginine vasopressin (AVP) levels; however, there is no concensus as to whether elevated AVP levels play a causal role in the pathophysiology of endotoxemia. The following studies were designed to evaluate the efficacy of a potent V_1 selective AVP receptor antagonist ([1-B-mercapto-B, B-cyclopentamethylene-proprionic acid, 2-(O-methyl)tyrosine-8-arginine vasopressin]; AVPRA) for limiting the responses of endotoxemia. At 0.5 and 1.0 hr after administration of 30 mg/kg i.v. of S. enteritidis endotoxin (LPS) to male Sprauge-Dawley rats, plasma AVP concentrations were increased to 175 and 130 pg/ml, respectively ($p < 0.01$, compared to the vehicle control group). Injection of LPS (n=10) resulted in a decrease in the survival rate to 20% (mean survival time: 22 ± 6 hr), an increase in heart rate of 84 bpm, a reduction in the circulating platelet count to 23% of the initial value, and an acute hemoconcentration that was maximal at 30 min after injection of LPS. In conscious rats, administration of AVPRA (1 - 100 µg/kg/hr i.v.) produced dose-dependent, parallel and rightward shifts in the AVP vasopressor dose-response curve: a 1,000-fold shift in the AVP dose-response curve was achieved with the highest dose of AVPRA. Administration of AVPRA (1 - 100 µg/kg/hr) beginning 15 min prior to the injection of LPS did not significantly limit any of the sequelae produced by endotoxemia. These results suggest that, in this model, antagonism of V_1 AVP receptors does not significantly improve the pathophysiology of endotoxemia.

164 7.5% NaCl/DEXTRAN 70 FOR PREHOSPITAL RESUSCITATION OF BLUNT TRAUMA. MJ Vassar*, CA Perry*, WL Gannaway*, GC Kramer, JW Holcroft. Univ. of Calif., Davis, CA 95616.

One hundred Life Flight trauma patients (85 blunt, 15 penetrating) with a systolic blood pressure ≤ 100 mmHg were entered into a randomized double-blinded trial to evaluate a 250 ml infusion of 7.5% NaCl/Dextran 70 versus lactated Ringer's. Results for the 85 patients with blunt injuries are shown in the table; 34 high-risk patients with a predicted survival of ≤0.25 were identified by the TRISS methodology.

	7.5% NaCl/Dex (N=43)		Lactated Ringer's (N=42)
Time from injury before infusion (min)	61±35(SD)		54±35(SD)
Revised trauma score before infusion	4.8±3.9		3.9±2.7
Injury severity score	33±17		35±18
Systolic BP before infusion (mmHg)	63±35		67±30
Transport time after infusion (min)	18±16		22±18
Fluid given during transport (L)	1.2±1.5		1.5±1.7
BP increase from baseline to ER admit	58±60	p=0.03	30±52
Predicted survival in all patients (TRISS)	58±41%		48±42%
Observed survival in all patients	27/43(63%)		21/42(50%)
Number of high-risk patients	15/43(35%)		19/42(45%)
BP before infusion in high-risk patients	48±32		58±32
BP increase from baseline to ER admit	55±63	p=0.05	13±58
Predicted survival high-risk patients (TRISS)	7±6%		6±7%
Observed survival in high-risk patients	5/15(33%)	p=0.01	0/19(0%)

Conclusion: Resuscitation with 7.5% NaCl/Dextran 70 significantly reversed hypotension and improved survival in patients with critical blunt injuries.

165 THE VASCULAR RESPONSE TO ADRENERGIC STIMULATION IN PITHED RATS FOLLOWING ENDOTOXIN. Z. Z. Zhou* and S B. Jones, Dept.of Physiology, Loyola University School of Medicine, Maywood, IL 60153.

Previous studies have shown reduced vascular responses to catecholamines after endotoxin (ETOX) treatment. Mechanisms of such attenuation may involve catecholamine-induced desensitization of adrenergic receptors. The present study assessed vascular responses to adrenergic stimulation after endotoxin treatment in pithed rats in which sympathetic stimulation is controlled,ETOX does not elevate norepinephrine (NE) and there are no reflex compensations to adrenergic stimulation. Rats were pithed (Gillespie and Muir, Br.J.Pharmac.30:78-87,1967), curarized and adrenal-demedulated. Preganglionic thoraco-lumbar nerves were stimulated (3Hz, 10v, 0.5msec) for 1 hr after pithing, followed by i.v. ETOX (1.5 mg/Kg) or saline and continued stimulation. The frequency response and dose response to NE was assessed 1 hr following ETOX or saline by measuring the peak increase in diastolic blood pressure (Δ DBP).

	Dose of NE (ng/Kg)	250	750	2500	7500	
	Saline Group	29±5	56±6	97±6	118±6	
Δ DBP	ETOX Group	12±2**	15±3*	26±2*	46±5.3*	
(X±SE	Fre. of Stim.(Hz)	1.0	2.0	4.0	8.0	
mmHg)	Saline Group	30±3	45±4	62±5	85±6	*P<.01
	ETOX Group	7±2*	12±3*	15±4*	26±5*	**P<.05

These results demonstrate decreased vascular responsiveness of pithed rats to adrenergic stimulation following endotoxin and suggests that mechanism other than an adrenergic desensitization may be involved. Supported by HL31163.

166 **PROTECTIVE EFFECTS OF A NOVEL NON-GLUCOCORTICOID 21-AMINOSTEROID (U-74006F) DURING TRAUMATIC SHOCK IN RATS.** Nobuo Aoki* and Allan M. Lefer. Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107.

The purpose of this study was to investigate the effect of the non-glucocorticoid steroid, U-74006F, in the pathogenesis of a murine traumatic shock model. Pentobarbital anesthetized (35 mg/kg, i.v.) rats were subjected to Noble-Collip drum trauma and developed a lethal shock state characterized by a mean arterial blood pressure (MABP) of 67 ± 2 mmHg and a mean survival time of 1.5 ± 0.2 h. In contrast, sham trauma rats exhibit a MABP of 122 ± 4 mmHg 5 hours post-anesthesia with all animals surviving. At 7.5 mg/kg U-74006F, survival time was 1.7 ± 0.3 h (NS from vehicle), at 15 mg/kg U-74006F, survival time improved to 2.5 ± 0.4 h ($p<0.05$) and at 22.5 mg/kg, U-74006F extended survival time to 3.1 ± 0.6 h ($p<0.02$). Administration of U-74006F (22.5 mg/kg) 15-20 min following trauma significantly maintained a higher MABP (109 ± 14 mmHg, $p<0.05$) than those receiving vehicle for U-74006F (0.002NHCl). At this dose, U-74006F also significantly attenuated the plasma accumulation of cathepsin D (6.9 ± 0.6 vs 15.6 ± 1.8 U/ml, $p<0.01$) and free amino-nitrogen compounds (6.8 ± 0.5 vs 10.4 ± 1.2 U/ml, $p<0.01$) compared to the rats receiving only vehicle. Additionally, U-74006F blunted the production of the cardiotoxic peptide, myocardial depressant factor (MDF) (36 ± 5 vs 88 ± 10 U/ml, $p<0.01$). Moreover, U-74006F, a steroid without significant glucocorticoid or mineralocorticoid activity, exerts a dose-dependent protective effect. These results suggest that U-74006F may be useful as a therapeutic agent in traumatic shock.

167 EFFICACY AND TOXICITY OF LAZAROID (U74006F) IN NEONATAL ENDOTOXEMIA S.D. Semrad, M.L. Rose*, M.L. Putnam*, School of Veterinary Medicine, University of Wisconsin-Madison, Madison WI 53706.

Lazaroids (21-aminosteroids) are effective inhibitors of lipid peroxidation. We studied their protective effects against sublethal endotoxemia in newborn calves. E. coli endotoxin (LPS: 3 ug/kg) in 200 ml of 0.9% saline was given by intravenous infusion over 3 hours. U74006F (U74: 1.5 mg/kg) was given intravenously over 5 minutes. Group A received LPS alone. Group B received U74 and a 3 hour infusion of 200 ml of 0.9% saline. Group C received LPS and U74 1 hour after beginning the LPS infusion. Group D received U74 1 hour before LPS. Clinical, hematologic, and chemical parameters were monitored over 24 hours. Group A calves became weak, recumbent, severely depressed, and developed

persistent diarrhea. Group C and D calves showed similar signs, but only transiently. All LPS treated groups were tachycardic and tachypneic. U74 protected against LPS-induced lactacidemia and hyperglycemia, but not leukopenia and hypoglycemia. U74 attenuated LPS-induced generation of thromboxane B_2 and prostacyclin. No significant changes were seen in Group B. Groups E, F, and G were given U74 (3 mg/kg) alone, LPS (increasing doses) alone or U74 and LPS, respectively, by intravenous injection every 8 hours for 5 days. At necropsy, no lesions were observed in Group E. Groups F and G had lesions consistent with endotoxemia but only Group G had evidence of abomasal and ruminal ulceration. U74006F may be a useful therapeutic agent in endotoxemia.

168 PLATELET ACTIVATING FACTOR (PAF) ANTAGONIST IMPROVES SURVIVAL AND ATTENUATES EICOSANOID RELEASE IN LETHAL ENDOTOXEMIA, J. Fletcher, M. Earnest*, J. Moore*, A. Disimone*, N. Abumrad*, Vanderbilt University Medical Center, Nashville, Tennessee 37232

PAF is a putative mediator in endotoxemia and sepsis. PAF releases eicosanoids. PAF receptor antagonists improve survival in rat endotoxemia. We hypothesized that a PAF antagonist, BN52021, would alter the hemodynamic events, attenuate the eicosanoid release and improve the survival in lethal canine endotoxemia. METHODS: Male dogs randomized: I (n=5), received only E. coli endotoxin (ENDO) 1 mg/kg IV; II (n=5) received BN52021, 5 mg/kg, IV (t-15 min), then ENDO. Animals resuscitated with saline. Hemodynamics, blood gases, TxB_2 measured at 0, 1-2, 60, 120, 240 mins. Survival determined at 72 hrs. All Grp I died; Grp II all lived ($p < 0.05$).

		0	1-2	120	240 mins
TxB_2	I	522±233	7162±1976*	4101±1436**	3268±936**
pg/ml	II	518±179	1731±1076	517±110	361±68
MAP	I	128±4	46±8**	93±7**	105±10
(torr)	II	117±9	47±3**	102±5	112±3

*$p < 0.05$, **$p < 0.02$; GI v GII (TxB_2); to baseline (MAP)

i) PAF antagonist improves survival and inhibits TxB_2 production in endotoxemia
ii) PAF is not related to early hypotension in endotoxemia
iii) PAF and eicosanoids may have an intimate relationship
iv) PAF may have a critical role in endotoxemia

169 **PROTECTIVE EFFECTS OF ACIDIFIED SODIUM NITRITE ($NaNO_2$) COMBINED WITH HUMAN SUPEROXIDE DISMUTASE (hSOD) IN MYOCARDIAL ISCHEMIA WITH REPERFUSION.** Gerald Johnson III, Philip S. Tsao* and Allan M. Lefer. Department of Physiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107.

An intact endothelium may be critical for the preservation of myocardial integrity in ischemia. We studied the effects of the combination of acidified $NaNO_2$, which releases nitric oxide (NO), identified as endothelium derived relaxing factor (EDRF), and hSOD in a 6 h cat model of myocardial ischemia (MI) and reperfusion. $NaNO_2$ (50 mmoles/kg/h) and hSOD (25 mg/kg/h) were infused starting 30 min post-occlusion of the LAD coronary artery followed by reperfusion one h later. Neither substance given separately at these doses had a significant effect on any dependent variable. Moreover, cardiac myeloperoxidase activity was significantly lower in $NaNO_2$ + hSOD treated cats than in MI + vehicle cats, signifying less neutrophil involvement. Creatine kinase activities in the MI + $NaNO_2$ + hSOD group (n=7) were significantly lower than the vehicle treated MI group (n=8) at every time beyond one hour ($p<0.05$). The area-at-risk expressed as % of total left ventricular weight was not significantly different between the MI + vehicle and MI + $NaNO_2$ + hSOD groups. However, the necrotic area expressed as a % of the myocardial area-at-risk was significantly lower than that observed in the vehicle treated cats (23.1 ± 3.9, 6.3 ± 2.5, $p<0.01$). In summary, the combination treatment of acidified $NaNO_2$ and hSOD exerts significant protection on the myocardium subjected to ischemia and reperfusion injury indicating that EDRF may have a cardioprotective effect in MI. hSOD acts synergistically with $NaNO_2$ to prolong the action of NO, by scavenging free radicals which have been shown to inactivate NO (EDRF). This intact endothelium may also attenuate neutrophil adhesion to the coronary vasculature.

170 EARLY POST BURN LIPID PEROXIDATION (EFFECT OF IBUPROFEN AND ALLOPURINOL). C. LaLonde* and R. Demling. Longwood Area Trauma Center at Beth Israel, Brigham and Women's, and Children's Hospitals, Boston, MA 02115.

We measured plasma lung and liver lipid peroxidation in anesthetized sheep after a 30% of total body surface, third degree burn. Animals were resuscitated to baseline filling pressures with Lactated Ringers and killed 10 hours post burn. Six sheep were pretreated with ibuprofen (12.5mg/kg) and five with allopurinol (50mg/kg). We used conjugated dienes and malondialdehyde as measures of lipid peroxidation. Circulating conjugated dienes increased from baseline of .48±.06 to .64±.05 after burn, while protein rich burn tissue lymph flow increased up to 8 fold. We also noted a significant increase in lung tissue malondialdehyde, MDA, from 45±4 to 60±6nMol/g and liver MDA from 110±20 to 271±34nMol/g along with increased tissue neutrophil sequestration. Ibuprofen attenuated lung tissue MDA but had not effect on lung inflammation, circulating lipid peroxides, or burn edema, indicating that ibuprofen most likely decreased O_2 radical release in lung tissue by the already sequestered neutrophils. Allopurinol, possibly via xanthine oxidase inhibition, markedly attenuated burn Q_L, circulating lipid peroxides, and prevented all pulmonary lipid peroxidation and inflammation, indicating that burn tissue oxidant release was in part responsible for local burn edema as well as distant inflammation and oxidant release, the latter most likely from complement activation. Neither antioxidant decreased the liver lipid peroxidation, indicating that its mechanism of production was different from that seen in burn tissue, plasma, or in the lung.

171 CROSS-LINKED HEMOGLOBIN SOLUTION AS A RESUSCITATIVE FLUID FOLLOWING HEMORRHAGE IN THE RAT. Diana Malcolm, Robert Przybelski* and David Burris*. Uniformed Services University of the Health Sciences, Bethesda, MD 20814, Walter Reed Army Institute of Research and Walter Reed Army Medical Center, Washington, D.C. 20307

Human cross-linked hemoglobin (HBXL) solution was used to resuscitate rats after a 20 ml/kg bleed under anesthesia. Rats (Sprague-Dawley, 300-350 g) were bled (20 ml/kg; 1 ml/min) from the femoral artery and reinfused (1.5 ml/min) via the jugular vein with shed blood (20 ml/kg), Ringer's Lactate (RL; 40 ml/kg) or 14% HBXL (10 and 20 ml/kg). Following hemorrhage, mean arterial pressure (MAP) dropped to 40% of baseline (100±5 mmHg); blood and both HBXL infusions promptly restored MAP to 150% of baseline. Within 15 min, MAP returned to baseline in the blood infused rats, but remained at 125% of baseline in the HBXL treated rats for at least 60 min. Heart rate (HR) which dropped to 60% of baseline (350±20 BPM) was returned to and remained at baseline values with both HBXL solutions and blood. RL infusion restored MAP and HR, however, its effects were transient (15 min) after which MAP and HR fell to 60% and 70% of baseline, respectively. Cutaneous pO_2 (Roche) fell to less than 5% of baseline (49.5±1.4 mmHg) following the bleed, and was quickly restored to baseline with both blood and HBXL. RL also restored pO_2 values to normal, however after infusion was complete, pO_2 values fell to 40% of baseline. Interestingly, 10 ml/kg of HBXL was as effective as 20 ml/kg in restoring and maintaining hemodynamics and tissue oxygenation. These findings suggest that HBXL is a useful blood substitute in acute, non-lethal hemorrhage. Furthermore, HBXL is as effective as blood in improving hemodynamics and tissue perfusion at half the volume of blood.

172 rCBF FOLLOWING FLUID RESUSCITATION FROM HEMORRHAGIC SHOCK WITH ISOTONIC OR 7.2% NACL WITH AND WITHOUT A SUBDURAL MASS. J. M. Whitley*, D.S. Prough*, D. Deal*, S. Vines*, and C. Taylor*. (Spon: G. Zaloga). Wake Forest Univ., Winston-Salem, NC 27103.

Hypertonic saline successfully restores hemodynamics with severe hemorrhage and lowers intracranial pressure (ICP). The lower ICP following resuscitation suggests an advantage in terms of restoration of cerebral perfusion and improved regional cerebral blood flow (rCBF). The purpose of this study was to compare the effects on rCBF following resuscitation from hemorrhage with isotonic or 7.2% NaCl with and without an intracranial mass. Experiments were carried out on ventilated dogs divided into two groups: Group I (n=12) were subjected to 30 minutes of hemorrhage by rapid removal of blood (MAP 50-55 mmHg), and then resuscitated with 56 ml/kg of 0.9% NaCl

(n=6), or 6.0 ml/kg of 7.2% NaCl (n=6). Group II (n=12) animals were prepared similarly with the addition of a subdural balloon inserted over the right parietal cortex and inflated to increase ICP to 15 mmHg prior to hemorrhage. rCBF was measured using radioactive microspheres before, during shock and following resuscitation for two hours. Brains were sectioned into 3 regions for analysis: right (RC) and left (LC) cerebral hemispheres and brainstem (BR). Group I rCBF values revealed no significant differences over time between fluid groups. Group II rCBF values were significantly different over time with 7.2% NaCl promoting higher blood flows in RC ($p=0.04$, by T test) and LC ($p=0.06$). BR values revealed no differences between fluid groups. These data demonstrate that 7.2% NaCl improves rCBF better than isotonic crystalloid when a subdural mass is present.

173 EFFECT OF IMPAIRED HEPATIC MITOCHONDRIAL FUNCTION (HMF) ON SYSTEMIC METABOLISM IN MULTIPLE ORGAN FAILURE (MOF) PATIENTS AND ITS TREATMENT WITH ATP-$MgCl_2$.
H. Hirasawa, T. Sugai*, Y. Ohtake, S. Oda*, H. Shiga*, T. Aoe* and M. Ohkawa Department of Emergency and CCM, Chiba University School of Medicine, Chiba, Japan 280

Previous study from our laboratory has shown that HMF is impaired among MOF patients. The present study was undertaken to investigate the effect of impaired HMF on systemic metabolism and the effect of ATP-$MgCl_2$ administration on HMF and systemic metabolism in MOF patients. In 88 MOF patients (45 survivors and 43 non-survivors) indirect calorimetry was performed using a metabolic computer while they were receiving TPN. Arterial ketone body ratio (AKBR) and blood levels of retinol binding protein and prealbumin were also measured. Non-protein respiratory quotient (npRQ) and energy burned as fat (%fat) were calculated from the data of indirect calorimetry. Some patients with impaired HMF received intravenous ATP-$MgCl_2$ administration (3000 μmole/kg) during TPN and the same parameters were studied. Non-survived MOF patients showed lower AKBR compared to postoperative controls and survived MOF patients. There were a significant positive correlation between AKBR and npRQ, and a significant negative correlation between AKBR and %fat, respectively, indicating that impaired HMF suppressed utilization of exogenous glucose. Blood levels of retinol binding protein and prealbumin showed significant positive correlations to AKBR. ATP-$MgCl_2$ administration increased AKBR and npRQ, and decreased %fat. These results indicate that impaired HMF adversely affects systemic energy metabolism and protein synthesis. The results also suggest a possible role of ATP-$MgCl_2$ as a metabolic modulator among MOF patients.

174 IMPROVED SURVIVAL FROM HEMORRHAGIC SHOCK WITH INOSITOL AND ATP-$MgCl_2$ ADMINISTRATION.
M.J. Shapiro*, M. Jellinek, B. Chandel, C. Tadros, A.E. Baue*. St. Louis University Medical Center, St. Louis, MO 63110

Phosphoinositides are structural components of membranes and hormonal receptor mediators. Hypovolemic shock may cause their loss and thus contribute to the mortality observed when hemorrhage occurs. In addition, in hypovolemic shock, the loss of ATP and the decline in ATP generating capacity intensifies such losses since phosphoinositide regeneration is dependent upon an adequate supply of ATP. Thus, in order to examine the effect of ATP, Inositol and ATP + Inositol administration on survival, 76 male Sprague-Dawley rats were anesthetized with 1.25 volume percent halothane. With additional local anesthesia, the right femoral artery was cannulated for continuous blood pressure recording. The left femoral artery was cannulated for blood withdrawal and infusion. The animals were awakened in a restraining cage. By withdrawing blood, 40mm Hg shock was maintained for 105 minutes. The blood was then reinfused and the animals received either placebo (15 ml/kg 0.9% N.S.), ATP-$MgCl_2$ (27 μmoles/kg/hr), Inositol (27 μmoles/kg/hr), or ATP-$MgCl_2$ + Inositol infused over one hour. The cannulae were then removed, and 24 hour survival recorded. Fifteen of 35 (43%) control animals survived, whereas 7 of 10 (70%) treated with ATP-$MgCl_2$ survived ($p > 0.1$). Twelve of 15 (80%) treated with Inositol survived ($< .02$), whereas 13 of 16 (81%) of the ATP-$MgCl_2$ + Inositol group survived ($p \leq .01$). The use of Inositol and ATP-$MgCl_2$ appear to be useful agents in improving survival from hemorrhagic hypovolemic shock.

175 EFFICACY OF POST-TREATMENT WITH ANTI-TNF MONOCLONAL ANTIBODY IN PREVENTING THE PATHOPHYSIOLOGY AND LETHALITY OF SEPSIS IN THE BABOON. L. Hinshaw, P. Olson* and G. Kuo*. Oklahoma Medical Research Foundation and Chiron Corporation, Oklahoma City, OK 73104.

Studies were carried out on 12 anesthetized baboons (cynocephalus) intravenously infused with LD_{100} E. coli for a two hour period. The aminoglycoside antibiotic, gentamicin was administered at designated times after the completion of E. coli infusion. Baboons were monitored for ten hours and observed until death or 7 days ("permanent survival"). Six animals received E. coli (5.1×10^{10} org/kg) and anti-TNF monoclonal antibody, 15 mg/kg 30 minutes after the onset of the E. coli infusion. Six animals received E. coli (5.9×10^{10} org/kg) and saline (N=3) or antibody carrier solution (N=3) in place of the antibody. All control animals died between 12 and 34 hours (mean, 19 hours) and in contrast, all animals treated with antibody to TNF survived greater than 7 days. Surviving baboons maintained more nearly normal values of arterial pressure, pH, glucose, cortisol, WBC, BUN, creatinine, SGPT, FDP and fibrinogen. The morphology of lungs, kidneys, adrenals, spleen, small intestine and colon were protected in all animals receiving the antibody to TNF. In conclusion, physiological, metabolic, host-defense and morphologic parameters were benefitted, and permanent survival was achieved in all baboons receiving LD_{100} E. coli and post-treated with antibody to TNF.

176 TEMPORAL RESPONSES OF CYTOKINES *IN VIVO* FOLLOWING INFLAMMATION AND TRAUMA IN HUMANS. J. Cannon*, J. Burke, C. Dinarello*, W. Evans*, R. Fielding*, J. Gelfand*, H. Michie*, R. Tompkins, D. Wilmore*, S. Wolff*. New Engl. Med. Ctr., USDA Nutr. Res. Ctr. on Aging, Tufts Univ., Brigham and Women's Hosp., Mass. Gen. Hosp., Boston MA.

Many of the metabolic, cardiovascular and immunological alterations which accompany infection or trauma are thought to be mediated, in part, by the cytokines interleukin-1β (IL-1β) and tumor necrosis factor/cachectin (TNFα). Our purpose was to define the temporal patterns of cytokine appearance *in vivo* and determine how various forms of inflammation or trauma influence these temporal patterns. In healthy subjects, plasma levels of each cytokine measured by radioimmunoassay were usually less than 75 pg/ml. Following i.v. infusion of 4 ng/kg of *E. coli* endotoxin in six normals, plasma IL-1β levels increased 37 ± 23 pg/ml by 180 min and plasma TNFα increased 852 ± 187 by 90 min, then rapidly returned to baseline. Following 45 min of eccentric exercise, which causes mild damage to contractile proteins and connective tissue, plasma IL-1β reached maximal increases of 58 ± 16 pg/ml after 3 to 9 hours in 9 subjects. Plasma IL-1β returned to baseline by 24 hours, but increased levels were detected in muscle tissue (by immunohistochemistry) for up to 5 days post-exercise. Following burn injury (30 - 85% body surface area, 10 patients), IL-1β and TNFα concentrations were elevated (>150 pg/ml) for up to 14 days; TNF levels tended to be maximal at 7 days. We conclude that plasma cytokine concentrations are elevated for a period of time which is determined by the rate at which an inflammatory stimulus is cleared or by the magnitude of an injury. In addition, tissue levels of cytokines can remain elevated after circulating levels have returned to baseline.

177 RELATIONSHIP OF TNFα TO BIOCHEMICAL, HEMATOLOGICAL AND SURVIVAL RESPONSE TO ENDOTOXEMIA IN CONSCIOUS RATS. G. Feuerstein, S. N. Vogel, B. Vanatta, J.M. Hallenbeck, Dept. of Neurology and Microbiology. USUHS 4301 Jones Bridge Road, Bethesda, Maryland 20814

Tumor Necrosis Factor (TNFα) is a recently discovered monocyte-macrophage derived monokine. TNFα has been implicated in mediation of endotoxic shock by virtue of its presence in the circulation in early stages of endotoxemia, its capacity to produce many manifestations of endotoxemia, and the ability of anti-TNFα antibodies to circumvent some of the responses to endotoxin. To clarify further the precise relationships of TNFα to survival and known hematological effects of endotoxin (ETX), Sprague-Dawley rats (275-300 g, n=5-15) were anesthetized (halothane 2%) and PE-50 catheter inserted into the femoral vein for a single injection of E. coli 0111:B4 ETX (0.001-28.8 mg/kg). The rats were allowed to recover and anesthetized again at 30, 60, 120, 180 min, 12 h or 3 days for a single aortic blood withdrawal for assay of TNFα (L929 bioassay), corticosterone (CS-RIA), platelet (P), WBC, and

hematocrit. Survival was studied in separate groups. The time course curve of TNFα showed a maximum increase 90-120 min after ETX and disappearance from the plasma at 6 hrs. The dose-response curve of TNFα showed maximum TNFα levels after 0.1 mg/kg ETX which caused only acute leukopenia (max at 2 hr, recovery at 24), late thrombocytopenia (max at 24, recovery at 72 hr), but no hemoconcentration. Plasma CS unlike TNFα showed a prolonged (> 12 hrs) and dose-dependent increase at all doses. None of the rats died up to ETX dose of 7.2 mg/kg. These data suggest that the TNFα response is associated with P and WBC depletion, but mortality in endotoxemia might be related to factors(s) other than TNFα.

178 CYTOKINE MEDIATED INCREASES IN VASCULAR PERMEABILITY (VP) IN VIVO. J.M. Hayes* and R.L. Simmons* (Spon: Frank Cerra). University of Pittsburgh, Pittsburgh, PA 15261.

Several cell types and their products have been implicated as mediators of the increased VP seen in sepsis. In order to study the local in vivo effects mediated by cytokines we injected rIL-1 and TNF into the hind footpad of Balb/c mice and 4 uCi of I^{125}Albumin(I^{125}A) intravenously. At various time points thereafter the hind feet were amputated, and the percent activity of injected I^{125}A in the hind feet was determined. The ratio of mediator to control footpad is the permeability index. Both rhIL-1(5U) and TNF(200U) induced significant increases in VP which peaked between 8 and 16 hours. Similarly, rmIL-1(alpha) also induced significant increases in VP, however, rmTNF(50-200U) had no effect. To determine whether these effects were due to direct interaction with the endothelium, or mediated through interactions with a circulating cell type, mice received 750 rads irradiation 72 hours prior to the experiment. Irradiation failed to influence the effect of rmIL-1 on VP.

	rhIL-1	rhTNF	rmIL-1	rmTNF
Permeability Index	1.52 ± .09	1.30 ± .03	1.76 ± .14	0.96 ± .1
p value vs unity	0.001	0.002	0.001	NS

These data suggest that in vivo VP may be mediated by direct cytokine-endothelial cell interaction.

179 THE ROLE OF PROTEIN SYNTHESIS IN STREPTOCOCCUS PNEUMONIAE (S pneu) INDUCED NEUTROPHIL (PMN) EMIGRATION INTO LUNGS. R. Winn, W. Mileski, C. Rice, and J. Harlan. University of Washington, Seattle, WA 98195

PMNs have been implicated in the developement of adult respiratory distress syndrome (ARDS) in critically ill patients. PMN adherence and formation of a protected microenvironment is thought to be one of the first events leading to tissue damage. Adherence and subsequent emigration is largely mediated by and interaction between the CD11/CD18 membrane complex on PMNs and endothelial cell adhesion molecules (some requiring de novo protein synthesis) and is blocked by the anti-CD18 monoclonal antibody (MAb) 60.3 . One exception is the lung when S pneu is used as the chemotactic agent. We asked the question: Is protein synthesis necessary for PMN emigration into lungs following airway instillation of S pneu or endotoxin (LPS). PMN emigration in the rabbit lung was examined under 3 conditions: 1) control (no treatment), 2) MAb 60.3 treated and 3) protein synthesis inhibition with cycloheximide (Cx). Two ml of saline containing either 20 ug of LPS or $2x10^9$ live S pneu were instilled into the trachea. After 4 hrs the animals were sacrificed and the left lung was lavaged with 10 ml of saline. Lavage PMN count in # PMNs/ml ± SD x 10^{-6} and percent inhibition (%) are given below.

	CONTROL	MAb 60.3	Cx
S pneu	1.84±0.95	0.87±0.54 (53%)	0.17±0.09 (91%)
LPS	4.48±3.44	0.88±0.60 (80%)	0.89±0.28 (80%)

These results suggest that PMN emigration toward S pneu is largely dependent on protein synthesis to produce either chemoattractants or adhesion molecules. Also the majority of PMN adherence in response to S. pneu is not CD18 dependent.

180 THE CARDIOVASCULAR AND PULMONARY EFFECTS OF HUMAN RECOMBINANT TUMOR NECROSIS FACTOR IN THE CONSCIOUS RAT. C. Turner*, K. Esser*, E. Wheeldon*, M. Slivjak* and E. Smith. Smith Kline & French Laboratories, King of Prussia, PA 19406-0939

In this study, the dose-response to a highly purified human recombinant tumor necrosis factor (TNF) preparation (1-2 x 10^7 U/mg; <0.05 ng endotoxin/mg TNF) was examined in the conscious rat. Rats received i.v. injections of 0.3 mg/kg (n=6), 1.0 mg/kg (n=17), 3.0 mg/kg (n=11) or 10 mg/kg (n=15) of TNF, 30 mg/kg (n=7) Salmonella enteridis endotoxin (LPS), or isotonic saline (n=11). Upon termination of the experiment, the lungs were removed for lavage or histology. Survival was 0% 24 h after LPS, and 83, 59, 73 and 73% after the lowest to highest doses of TNF, respectively. TNF caused a dose-dependent increase in heart rate ($p<0.05$) within 0.5 h of exposure which remained elevated throughout the 24 h period. TNF had no effect on mean arterial blood pressure (MABP) acutely, but caused a 15-20% decrease in MABP 24 h post exposure ($p<0.05$). TNF increased hematocrit in all dose groups by 10-15%. Furthermore, TNF produced a thrombocytopenia in all dose groups within 1-3 h, and TNF doses of 1-10 mg/kg caused a leukopenia within 0.5 h ($p<0.05$). Lavage and histology revealed no changes in the number of pulmonary neutrophils. These results suggest that TNF stimulated dose-dependent responses were consistent with those produced by LPS. However, these responses were appreciably smaller than those reported for either LPS or for TNF from other sources. One possible explanation for our anomalous findings may be the unusually low level of LPS contamination in our material, a factor which has recently been shown to act synergistically with TNF (Proc Natl Acad Sci USA,85:607-611,1988).

181 AN ALTERATION IN EARLY T-LYMPHOCYTE ACTIVATION FOLLOWING TRAUMA

D. Hoyt* and N. Ozkan* (Spon: S.R. Shackford). University of California, San Diego Department of Surgery H-640B San Diego, California 92103

Tissue inflammation with elastase mediated proteolysis can generate matrix protein degradation products with immunoregulatory properties. Previous studies have shown a low molecular weight glycopeptide enriched from elastase digested human cellular fibronectin (FNDP) impairs T cell activation and proliferation and is reversible by the Ca++ ionophore A23187. The purpose of this experiment was to investigate whether the generation of inositol triphosphate (IP3), essential for T-cell cytosol Ca++ mobilization was inhibited. Human PBLs were pretreated with H^3 inositol and incubated with FNDP or buffer control and stimulated with PHA. Inositol turnover was measured after 5, 10, and 15 min. Results are expressed as percent inhibition of control for each time period.

	Percent Inhibition	
	IP2	IP3
Five Min.	59%	12%
Ten Min.	20%	48%
Fifteen Min.	11%	81%

The formation of IP3 essential for intracellular Ca++ release with subsequent activation of protein kinase is impaired at fifteen min, and suggests a mechanism by which a trauma associated inflammation might impair T-cell activation and cause immunosuppression.

182 ENDOTHELIN: AN ENDOTHELIAL-DERIVED PEPTIDE WITH POSITIVE INOTROPIC ACTION IN ARTERIAL SMOOTH MUSCLE AND MYOCARDIUM.

J.A. Allert*, C. Wagner-Mann*, M. Sturek*, and H. R. Adams. Univ. Missouri, Columbia, MO 65211

Endothelin (ET) is a recently discovered 21 amino acid peptide synthesized by vascular endothelial cells (VEC) and believed to be: (1) the most potent endogenous vasoconstrictor yet discovered, and (2) the endogenous agonist ligand for voltage-gated Ca^{++} channels of the cell membrane (Nature 332:415,1988). We tested the hypothesis that ET exerts cardiovascular actions via mechanisms other than just Ca^{++} channel activation. ET induced inotropic effects in electrically paced atrial myocardium of guinea pigs, increasing isometric contractile tension by 62% above basal values with an $EC_{50} \simeq 1.0$ nM (n=8). However, ET did not restore mechanical activity to K^+ depolarized (22mM;n=6) or tetrodotoxin-poisoned (30μM;n=6) heart muscle, suggesting that ET did not activate quiescent Ca^{++} channels. We also tested ET in freshly dispersed single coronary artery smooth muscle cells (SMC) from pigs, and measured intracellular Ca^{++} (Ca_i) with fura-2 microfluorimetry. ET enhanced the high K^+(80mM)-induced increase in Ca_i by 2-fold, consistent with a Ca^{++} channel ligand action. However, the ET evoked increase in Ca_i in normal K^+ solution (5.0mM) was attenuated only by 50% by either Ca^{++}-free media or 0.2mM lanthanum, suggesting that ET can release Ca^{++} from intracellular storage sites such as the sarcoplasmic reticulum. Thus, ET

may activate SMC and heart muscle via intracellular Ca^{++}-dependent mechanisms as well as by Ca^{++} channel ligand actions. Since ischemia and different types of shock injure VEC with release of VEC products, we hypothesize that ET may prove to be an important endothelial-derived vasoconstrictor factor and positive cardiac inotrope that could account for regional vasoconstriction and perhaps cardiac contractile adjustments during tissue ischemia and/or shock.

183 EVIDENCE FOR ENDOTOXIN RELATED TUMOR NECROSIS FACTOR (TNF) RELEASE IN INTESTINAL ISCHEMIA-REPERFUSION INJURY MG Caty*, DG Remick*, DJ Schmeling*, S Kunkel*, KS Guice, KT Oldham, University of Michigan Medical School, Ann Arbor, MI 48109.

Endotoxin mediates the in vitro release of TNF. Intestinal ischemia - reperfusion injury is associated with bacterial translocation and endotoxemia. This study was designed to evaluate TNF release and endotoxemia in intestinal ischemia-reperfusion injury. METHODS: 100-150 gram Sprague-Dawley rats were subjected to intestinal ischemia by occlusion of the superior mesenteric artery by a microvascular clip. Reperfusion for 15, 30, and 60 minutes was achieved by removal of the clip at a second laparotomy. At sacrifice portal vein plasma was obtained for endotoxin determination (chromagenic limulus assay) and systemic plasma was obtained for TNF measurement using the WEHI 164 subclone 13 cell line. RESULTS:

TREATMENT	TNF(U/ml)	ENDOTOXIN (EU/ml)
0/0 (Sham)	0.13 ± 0.09	---
30/0	----	0.075 ± 0.01
60/0	0.02 ± 0.01	0.074 ± 0.01
120/0	1.19 ± 0.50	0.160 ± 0.04
120/15	6.61 ± 3.11	----
120/30	10.41 ± 5.41*	0.290 ± 0.005
120/60	1.92 ± 1.58	----

* $p < .05$ compared to sham by Newman-Keuls Test

(TREATMENT = ischemia in min/reperfusion period; eg 120 min. ischemia/x min reperfusion). Intestinal ischemia results in portal vein endotoxin release followed by significant elevations in circulating TNF levels. Endotoxin from this intestinal injury may play a pathogenic role in the systemic release of TNF.

184 THE ROLE OF TOXIC OXYGEN METABOLITES IN THE PATHOGENESIS OF A NEW MODEL OF ACUTE HEMORRHAGIC AND NECROTIC PANCREATITIS. T. L. Yang,* M. S. Sussman,* G. B. Bulkley, and J. L. Cameron.* Department of Surgery, The Johns Hopkins Medical Institutions, Baltimore, MD 21205.

Free radical ablation blocks the manifestations of acute pancreatitis in some, but not other animal models of this disease. We have previously found that the infusion of oleic acid into the isolated, perfused, ex vivo canine pancreas, mimicking alcoholic hyperlipidemia, produces edema and hyperamlyasemia, signs of early acute pancreatitis that were both significantly reduced by free radical ablation. We adopted this model to an in vivo rat preparation by the infusion of 90 mg of oleic acid in 0.5 ml 1.09% Tween-20 in saline/h for 6h into the pancreatic (tail) branch of the superior mesenteric artery. This produced not only localized edema (pancreatic H_2O content ↑'d from 76.8±0.3 to 80.2±0.6%, $p<.05$ vs vehicle alone*) and hyperamylasemia (serum amylase ↑'d from 3062 ± 521 to 5547 ±345 u/dl*) at 24h (analogous to the previous ex vivo results). This progressed to frank pancreatic necrosis and (sterile) abscess formation over the next 48 hours. Scavenging superoxide free radicals with superoxide dismutase and catalase reduced this early hyperamlyasemia to 3173 ± 186 u/dl (↑$p<.05$ vs oleic acid). Similarly, blocking superoxide generation from xanthine oxidase with allopurinol reduced the hyperamlyasemia to 4282 ± 430 u/dl↑. Neither treatment had a significant effect on the subsequent development of hemorrhage or necrosis. These findings suggest that toxic oxygen metabolites generated from activated xanthine oxidase play a major role in the acute hyperamlyasemia, but not the subsequent hemorrhagic necrosis seen in this new model of the full spectrum of acute pancreatitis.

185 OXYGEN-RADICAL-MEDIATED ACUTE LUNG INJURY: ENHANCEMENT OF XANTHINE OXIDASE ACTIVITY BY HISTAMINE. H.P. Friedl, G.O. Till, P.A. Ward, O. Trentz. Univ. of Michigan, Ann Arbor, MI 48109-0602 and Univ. of Saarland, D-6650 Homburg, FRG.

We have previously shown that acute lung injury in the rat following systemic complement activation by cobra venom factor (CVF) is mediated by oxygen radicals (hydroxyl radical) derived from blood neutrophils as well as from xanthine oxidase (XO). We now have obtained evidence to suggest that histamine plays a critical role in this model of pulmonary injury. Examination of plasma samples obtained at different time points after CVF injection revealed a striking increase in plasma XO activity which was paralleled by an increase in plasma histamine levels. XO activity (determined by uric acid formation and O_2^- generation from added xanthine in the presence of the uricase inhibitor oxonate and +/- NAD^+) as well as histamine levels (RIA) peaked at 10 min post CVF reaching values of approximately 29 nmoles/ml/min and 900 nM, respectively. Plasma XO levels remained unchanged. The dose-dependent, potentiating effect of histamine on plasma XO activity could be duplicated in vitro. Prevention of the rise in histamine levels by pretreatment of experimental animals with cromolyn sodium (20 mg/kg) inhibited the increase of XO activity in post-CVF plasma and attenuated the acute lung injury. Our data suggest that histamine has a modulating effect on XO activity and may thus affect the production as well as the tissue-damaging effects of oxygen radicals. (Supported in part by NIH grants GM39397, GM28499, GM29507 and a grant from the Deutsche Forschungsgemeinschaft FR744/1-1).

186 OXYGEN FREE RADICALS (OFRs): THE RENAL HEMODYNAMIC RESPONSE. J.Galat*, A.Robinson*, R.Rhodes. Case Western Res. U., Cleveland, OH 44106 & U. of Miss., Jackson, MS 39216

Postischemic renal dysfunction (PIRD) is characterized by a decrease in glomerular filtration out of proportion to the decrease in renal flow. This study utilized isolated rat kidneys perfused at 37°C and 90-100 mm Hg with a modified Krebs' buffer to determine the contribution of OFRs. Kidneys were divided into the following groups (each N=8): I, time matched controls; II, infusion of 25 μmoles of hypoxanthine (H) and 1 unit of xanthine oxidase (XO) to generate OFRs: III, H and XO after prior treatment with OFR scavengers (250 units superoxide dismutase and 500 units catalase per ml buffer). In Part A, vascular resistance (VR), perfusate flow rate (PFR), glomerular filtration rate (GFR), and filtration fraction (%FILT) were measured 40 min after infusion of H and XO. In Part B, the kidneys were fixed and the area of Bowman's capsule occupied by the glomerular tuft (%TUFT) was determined by computerized morphometric techniques.

Group		VR	PFR	GFR	%FILT		%TUFT
I		2.9±.1	335± 6	4.8±.2	1.42±.07		78.5± .9
II	Part A	4.3±.3***	237±13***	1.4±.4***	.61±.17***	Part B	75.1±1.0**
III		3.1±.1	310±13	4.6±.3	1.47±.10		79.1± .9

(Mean±SEM; VR=mm Hg/(ml/min/g), flows=μl/min/g; **=p<.01, ***=p<.001 vs. Groups I & III by ANOVA and the Newman-Keuls test)

OFR generation caused a decrease in GFR out of proportion to the decrease in PFR (decreased %FILT). OFRs may contribute to the hemodynamic alterations observed with PIRD by causing glomerular contraction (decreased %TUFT) not previously recognized.

187 HEPATIC PERFUSION ABNORMALITIES PRODUCED BY SYNERGISM BETWEEN PLATELET ACTIVATING FACTOR (PAF) AND COMPLEMENT. William J. Schirmer*, James M. Schirmer*, Donald E. Fry, Department of Surgery, Case Western Reserve University, VAMC, Cleveland, OH.

In recent studies we found that hepatic perfusion during endotoxemia improved following either complement depletion or treatment with PAF-receptor antagonists. Yet, neither low doses of PAF nor experimental complement activation by slow infusion of cobra venom factor (CVF) produce the reduction in hepatic flow seen during endotoxemia. This study examines whether synergism between PAF and complement alters organ blood flow. Rats were divided into four groups (n=8) to receive 30 min IV infusions of either: I) saline, 1.0 mL/kg; II) CVF, 20 units/kg; III) PAF, 0.25 mg/kg, or IV) CVF plus PAF, aforementioned doses. At t=2 hrs, thermodilution cardiac output (CO), mean arterial pressure (MAP), heart rate (HR), hepatic blood flow (HBF) by galactose clearance, renal plasma flow (RPF) by PAH clearance, and the % change in total hemolytic complement (CH50) from t=0 to t=2 hrs were determined. The data are:

GROUP	CO	MAP	HR	HBF	RPF	%ΔCH50
SALINE	36.8±1.5	104±6	296±13	5.58±0.34	3.73±0.38	-7±4
CVF	35.4±1.6	96±4	290±14	5.36±0.35	3.42±0.16	-79±2#
PAF	38.4±1.8	103±7	291±11	5.74±0.42	4.04±0.36	-6±5
CVF+PAF	35.9±1.8	106±8	286±10	4.67±0.29*	3.46±0.15	-76±2#

*p<0.05 or #p<0.001 vs SALINE by ANOVA and Newman-Kuels multiple range test.
Data as mean(±SEM). Units: flows = mL/min/100 gm b.w.; MAP = mmHg; HR = beats/min.

This study suggests that synergism between liberated PAF and activated complement during endotoxemia and sepsis may contribute to the associated reductions in HBF.

188 ROLE OF IRON IN ISCHEMIA AND REPERFUSION. E.Robinson and B.Hedlund*, University of Minnesota, St.Paul, MN 55108; *Biomedical Frontiers,Inc., Minneapolis, MN 55414. Several investigators have demonstrated that in hemorrhagic shock, i.e. global ischemic state, there is release of iron from intracellular storage sites into circulation. This iron may derive primarily from the ischemic liver.'In vitro' evidence suggests this iron derives from ferritin by means of reduction by superoxide ion.We wanted to determine if this phenomenon was unique to the liver, or if similar molecular events occur in other ischemic organs. A rat model of 90 minutes of complete intestinal ischemia followed by reperfusion was used. Control sham-operated rats had either abdominal incisions, or exteriorization of intestines alone,in the absence of ischemia. Results indicated significant increases in transferrin-bound iron 60 and 120 minutes after the start of reperfusion(37.9,49.0 uMFe) compared to pre-ischemic, ischemic and sham control rats(28.4, 28.8 and 32.1 uMFe). To test the theory that iron release may be involved in mortality from ischemia-reperfusion insult to intestines, the iron chelator, deferoxamine (DFO), was tested for its therapeutic effect. Two forms of DFO were used; free drug, and a high molecular weight version of the drug obtained by covalent attachment of DFO to hydroxyethyl starch (DFO-HES). Four groups of animals were tested, using the 90-minute intestinal ischemia model. The following mortalities were obtained: Group I(saline):67% (n=9); Group II(HES):67% (n=9), Group III(free DFO 100md/kg in HES):89%* (n=9), Group IV(DFO-HES):44%*(n=9)(*sig.diff.p 0.05). The results indicate that the iron chelator, deferoxamine, conjugated to colloid may afford better protestion against reperfusion injury than either the colloid alone or colloid used in conjunction with free drug.

Author-Abstract Index

Directory

THE SHOCK SOCIETY

OFFICERS OF THE SOCIETY
1988–1989

President

John J. Spitzer, MD, Louisiana State University Medical Center

President-Elect

Frank R. Lewis, MD, San Francisco General Hospital

Secretary

Judy A. Spitzer, PhD, Louisiana State University Medical Center

Treasurer

John T. Flynn, PhD, Jefferson Medical College

Executive Director

Sherwood M. Reichard, PhD, Medical College of Georgia

Editor, Circulatory Shock

James P. Filkins, PhD, Loyola University Medical Center

Council

Ronald V. Maier, MD, University of Washington
Curtis Wise, PhD, Medical University of South Carolina
Daniel L. Traber, PhD, Shriners Burns Institute
Bart Chernow, MD, Harvard Medical School
James A. Cook, PhD, Medical University of South Carolina
Charles L. Rice, MD, University of Washington
Gerald S. Moss, MD, Michael Reese Hospital

Program Chair

Irshad H. Chaudry, PhD, Michigan State University

PAST OFFICERS

President

William Schumer, MD, 1978–1979
James P. Filkins, PhD, 1979–1980
Bryan E. Marshall, MD, 1980–1981
Sherwood M. Reichard, PhD, 1981–1982
Arthur E. Baue, MD, 1982–1983
Allan M. Lefer, PhD, 1983–1984

J. Raymond Fletcher, MD, PhD, 1984–1985
Lerner B. Hinshaw, PhD, 1985–1986
David G. Reynolds, PhD, 1986–1987
Gerald S. Moss, MD, 1987–1988
John J. Spitzer, MD, 1988–1989

President-Elect

James P. Filkins, PhD, 1978–1979
Bryan E. Marshall, MD, 1979–1980
Sherwood M. Reichard, PhD, 1980–1981
Arthur E. Baue, MD, 1981–1982
Allan M. Lefer, PhD, 1982–1983
J. Raymond Fletcher, MD, PhD, 1983–1984
Lerner B. Hinshaw, PhD, 1984–1985
David G. Reynolds, PhD, 1985–1986
Gerald S. Moss, MD, 1986–1987
John J. Spitzer, MD, 1987–1988
Frank R. Lewis, MD, 1988–1989

Secretary

Sherwood M. Reichard, PhD, 1978–1980
Leena M. Mela-Riker, MD, 1980–1985
Judy A. Spitzer, PhD, 1985–1989

Treasurer

David G. Reynolds, PhD, 1978–1984
John W. Holaday, PhD, 1984–1988
John T. Flynn, PhD, 1988–1989

MEETINGS

National Meetings

1st June 1–3, 1978, Airlie, Virginia
William Schumer, MD, Chair
Abstracts: Circulatory Shock 5:2, 183–232, 1978
Papers: Advances in Shock Research, Vols. 1 & 2, 1979, and Metabolic and Cardiac Alterations in Shock and Trauma. Circulatory Shock, Supplement 1, 1979

2nd June 7–9, 1979, Williamsburg, Virginia
David G. Reynolds, PhD, Chair
Abstracts: Circulatory Shock 6:2, 165–198, 1979
Papers: Advances in Shock Research, Vols. 3 & 4, 1980

3rd June 11–13, 1980, Lake of the Ozarks, Missouri
Lerner B. Hinshaw, PhD, Chair
Abstracts: Circulatory Shock 7:2, 187–223, 1980
Papers: Advances in Shock Research, Vols. 5 & 6, 1981

4th June 4–6, 1981, Marco Island, Florida
Sherwood M. Reichard, PhD, Chair
Abstracts: Circulatory Shock 8:2, 1981
Papers: Advances in Shock Research, Vols. 7 & 8, 1982

5th June 9–11, 1982, Smuggler's Notch, Vermont
Robert R. Wolfe, PhD, Chair
Abstracts: Circulatory Shock 9:2, 1982
Papers: Advances in Shock Research, Vols. 9 & 10, 1983

6th June 6–8, 1983, Grand Teton National Park, Wyoming
Robert W. Phillips, PhD, Chair
Abstracts: Circulatory Shock 10:3, 1983

7th June 4–6, 1984, Toronto, Canada
Glen A. Taylor, MD, Chair
Abstracts: Circulatory Shock, 13:1, 1984

8th June 9–12, 1985, Baltimore, Maryland
Daniel L. Traber, PhD, Chair
Abstracts: Circulatory Shock, 16:1, 1985

9th June 8–11, 1986, Scottsdale, Arizona
Gerald S. Moss, MD, Chair
Abstracts: Circulatory Shock, 18:4, 1986

10th June 7–11, 1987, Montreal, Canada
Robert F. Bond, PhD, Chair
Abstracts: Circulatory Shock, 21:4, 1987

11th June 5–8, 1988, Lake Geneva, Wisconsin
John C. Passmore, PhD, Chair
Abstracts: Circulatory Shock, 24:4, 1988

12th June 9–12, 1989, Marco Island, Florida
Irshad H. Chaudry, PhD, Chair

INTERNATIONAL CONGRESSES

1st June 7–11, 1987, Montreal, Canada
Robert F. Bond, PhD, Chair
Abstracts: Circulatory Shock, 21:4, 1987

2nd Proposed 1991, Vienna, Austria
Gunther Schlag, MD, Chair

July 10–24, 1980, Budapest, Hungary
Cosponsors: Shock Society and International Congress of Physiology
Arisztid G.B. Kovach, John J. Spitzer, and H.B. Stoner, Chairs
Papers: Advances in Physiological Sciences, Vol. 26, Homeostasis in Injury and Shock, Pergamon Press, 1981

September 5–8, 1984, Manchester, England. "The Scientific Basis of the Care of the Critically Ill," M.H. Irving and R.A. Little, Chairs
Partially supported by the Shock Society.

Constitution

CONSTITUTION OF THE SHOCK SOCIETY

ARTICLE I (Name)

The name of the society shall be the SHOCK SOCIETY.

ARTICLE II (Purpose)

The purpose of the Society shall be:

1. To promote original research in the fields of Shock and Trauma.
2. To provide a forum for the multidisciplinary integration of current basic and clinical knowledge and concepts in the study of shock and trauma.
3. To promote the dissemination and applications of knowledge of these fields.
4. To promote an awareness of the national and international health importance of shock and trauma.

ARTICLE III (Membership)

Membership in the Society shall be open to persons who share the stated purpose of the Society and who have educational, research, or clinical experience in the field of shock and trauma or in an allied discipline.

ARTICLE IV (Officers)

The officers of the Society shall be a President, a President-Elect, a Secretary, and a Treasurer. The President-Elect shall serve one year as such, followed by one year as President. No person shall ever be eligible for re-election to the Presidency.

The Secretary and Treasurer shall be elected to terms of two years. The Secretary will be elected on odd years and the Treasurer on even years. No person may hold the offices of Secretary and Treasurer for more than two terms.

ARTICLE V (Council)

There shall be a Council responsible for the fulfillment of the scientific and business obligations of the Society.

The current Officers, the immediate Past-President, the Editor(s) of the official Society Journal—Circulatory Shock, the Chair of the Scientific Program Committee, and six additional Councilors shall constitute this Council. Councilors shall be elected to provide representation from the various subdivisions of shock research. Councilors shall be chosen by the membership of the Society for three-year terms, two to be

elected each year. No Councilors shall be eligible for re-election until one year after the expiration of a full three-year term. Upon the recommendation of the Publications Committee, the Editor(s) will be elected by the Council for a four-year term and may be immediately eligible for re-election.

ARTICLE VI (Affiliations)

The Society is empowered to affiliate with other organizations.

Proposals for affiliation may be initiated by individual Members of the Council or by a petition to the Council signed by ten Members of the Society, and to become effective must be approved by a two-thirds majority of the Council and approved by the membership.

ARTICLE VII (Bylaws)

The provisions of the Constitution of the Society shall be carried out in accordance with the current Bylaws of the Society.

ARTICLE VIII (Amendments)

Amendments may be initiated by individual Members of the Council or by a petition to the Council signed by ten Members of the Society. Amendments must be approved by a two-thirds majority of the Council, must then be discussed at a subsequent business meeting of the Society, and must finally be ratified in a mail ballot by a majority of those Members of the Society voting.

ARTICLE IX (Dissolution)

Dissolution of the Society for any cause shall be initiated by individual Members of the Council or by a petition to the Council signed by ten Members of the Society. Such motion or petition must be approved by a two-thirds majority of the Council, must then be discussed at a subsequent business meeting of the Society, and must finally be ratified in a mail ballot by two-thirds of those Members of the Society voting. Dissolution must be in accordance with the applicable regulations of the 1965 Internal Revenue Code, Section 506, or any amendments thereto.

All funds and other assets of the Society, including any rights to funds, present or future, contingent or actual, shall be irrevocably assigned and transferred to any successor society which has among its principal purposes the encouragement, development, and dissemination of knowledge in the biological or physical sciences, and has qualified as an exempt organization under Section 501 of the 1954 Internal Revenue Code. Such activities or any amendments thereto need not be the only purpose of the successor society.

The selection of the successor society must be approved by a two-thirds vote of the Council and named in the Council's minutes and its Articles of Dissolution, but need not be named in the motion of petition for dissolution.

BYLAWS*

ARTICLE I (Membership)

1. The membership of the Society shall consist of Members (including Charter Members), Student Members, Associate Members, Emeritus Members, and Sustaining Members.

2. Members. A person who shares the stated purpose of the Council and is eligible under Article III of the Constitution may be elected a Member. Applicants must be sponsored by two Members. Applications must be submitted to the Society office and will then be transmitted to the Membership Committee for approval.

3. Student Members. The principal requirement for Student Membership is a genuine and active interest in the aims and purposes of the Society. Applicants must be sponsored by an active member of the Society. The fee for Student Membership shall be the Society's cost of the Journal, Circulatory Shock, or 1/2 of the Society's dues without the Journal. Membership shall be renewable each year for a maximum of 5 years. Application for Full Membership in the Society is then required. Student Membership does not include voting privileges in the Society. Student Members may submit one paper at the Annual Meeting without Full member sponsorship, but may not sponsor any papers at the Annual Meeting.

4. Associate Members. The principal requirement for Associate Membership is a genuine and active interest in the aims and purposes of the Society. Applicants must be sponsored by an active member of the Society. The fee for Associate Membership shall be more than that for full members, but less than the subscription rate for non-members. Application for Full membership in the Society may be made whenever an appropriate degree of experience or publications has been achieved. Associate Membership does not include voting privileges in the Society. Associate Members may submit one paper at the Annual Meeting without Full member sponsorship, but may not sponsor any papers at the Annual Meeting.

5. Emeritus Members. A Member who has retired or become emeritus may apply to the Council for election to emeritus status. Emeritus Members shall pay no dues but shall have all rights and privileges of Members.

6. Sustaining Members. The Council may elect a person or corporation a Sustaining Member as a result of demonstrated and substantial acts benefitting the Society or its purposes. Only in the case of a person qualified as a Member may a Sustaining Member vote or hold office.

ARTICLE II (Meetings)

The Society is authorized to hold scientific meetings, international, national, and regional. A business meeting shall be held in connection with the annual scientific meeting of the Society. Parliamentary procedures to be followed in the business meeting shall be those specified in "Robert's Rules of Order." Five percent of the Members, or 50, whichever is smaller, shall constitute a quorum.

*Amended January, 1983; June, 1986; June, 1987; June, 1988.

ARTICLE III (Dues)

All fiscal affairs of the Society shall be conducted on the basis of the calendar year.

Membership dues may be changed by the Council, subject to approval at the next annual business meeting.

Annual dues are payable on October 1st preceding the beginning of the fiscal year. Members who have not paid by December 1st will be notified and if they still have not paid by the first day of the fiscal year they will be dropped from the mailing list. Prior to the following April 1st, Members will be reinstated upon payment of dues; if in arrears on that date, they will be dropped from membership.

ARTICLE IV (Publications)

The Society is empowered to publish or to enter into agreements with others to publish such journals and other publications (abstracts, reviews, newsletters, etc.) as may be authorized by a two-thirds majority vote of the Council. Changes in the agreements which implement the publishing of a duly established journal or other organ may be authorized by a majority vote of the Council.

ARTICLE V (Duties of Officers)

It shall be the duty of the President to preside over the annual business meeting of the Society, to serve as chair of the Council, to appoint and charge, with the approval of the Council, the Chair and members of all committees of the Council, and to carry out other activities usually pertaining to the office.

The President-Elect shall carry out the duties of an absent or disabled President. The President-Elect will automatically succeed to the presidency when the office becomes vacant.

The Secretary shall keep accurate records, maintain an up-to-date membership list, and give notice of all meetings of members and of the Councils.

The Treasurer shall send out dues notices and collect all dues. He shall be responsible for all funds and securities of the Society, and shall make all disbursements in accordance with the budget approved by the Council. He shall submit an annual report of the financial condition of the Society and be responsible for any financial reports required by the Internal Revenue Service.

ARTICLE VI (Duties of the Council)

The duties of the Council shall be to determine the policies for the good of the Society and the science it represents in accordance with the Constitution and to implement the execution of these policies as provided in these Bylaws. It shall plan scientific meetings; it shall authorize the expenditure of Society funds, and it shall obtain an annual audit of the Society finances.

The Council shall fill a vacancy in the offices of Secretary and Treasurer until the office can be filled by a regular election of the Society; and in the event that the presidency becomes vacant when there is no President-Elect, it shall elect one of its numbers as Acting President until a regularly elected President takes office.

Interim vacancies among the Councilors may be filled by the Council until the next regular election of the Society.

Upon the recommendation of the Publications Committee, Council shall elect the Editor(s) of its official journal(s) by a two-thirds majority vote.

The Council may, if it deems necessary, appoint an Executive Secretary with appropriate compensation to assist in handling the affairs of the Society.

The Council may, at its discretion, appoint an Executive Committee from its members and may delegate to this committee such powers as it sees fit.

The Council shall meet, at the call of the President, at least once a year. At the regular meeting it shall consider changes in dues, amendments to the Constitution and Bylaws, and proposals for affiliation, and set the agenda for the business meeting. Newly elected Council members who have not yet taken office, are expected to attend this meeting, but may not vote. The Council shall have power to conduct other business by means of mail vote.

Six voting Members of the Council shall constitute a quorum.

The Council may apply for grants or secure donations for specific projects which are consistent with the purposes of the Society and they or appropriate Committees of the Council may then meet to consider their business at times other than the Annual Meeting with expenses defrayed by said grants or donations.

ARTICLE VII (Elections)

Nominations for offices to become vacant shall be made by the nominating committee. Nominations will also be received by petition. Each petition must be signed by ten Members and must contain a written statement by the nominee of willingness to serve. In order that the names of persons so nominated may appear on the ballot, petitions must be received by the Secretary before January 1st. The final list of nominees arranged as a ballot, and containing more than one name for each vacancy to be filled, shall be mailed to the Members. The candidate for each office receiving the highest number of votes will be elected.

The election of Councilors shall follow the same schedule as for the election of officers. The slate of the nominating committee shall contain at least one more name than the number of vacancies for both full and unexpired terms. Additional nominations for Councilor may be made by petition. Each petition must be signed by five Members and must contain a written statement of willingness to serve.

All officers and Councilors shall take office at the end of the annual business meeting.

ARTICLE VIII (Standing Committees)

1. Awards and Honors Committee. The Awards and Honors Committee shall normally be composed of three members, two of whom are Past-Presidents of the Society. Each President appoints one member to a three-year term and designates the Chair of the Committee. The Committee is charged with the responsibility for selecting finalists from the abstracts entered by students in training (Predoctoral or Postdoctoral). Finalists will present their work at the Annual Meeting. The Committee may also be charged with selecting a member of the Society who has shown consistent

excellence in research. The award will be a named award. Any recommendation for new awards and honors made by the Council or membership will be referred to this Committee for discussion and recommendation. This Committee can also initiate recommendations and other ideas for Awards and Honors appropriate to the goals and objectives of the Society.

2. Development Committee. The Chair of the Development Committee shall be appointed for a three-year term and shall be a member of the Finance Committee. The Chair, with the consent of the President, may appoint additional members to the Committee as needed. The Development Committee is responsible for (1) developing plans for the Society over the next few years, (2) coordinating Society activities affecting corporations, (3) soliciting sustaining members, (4) recommending benefits for sustaining members, (5) coordinating the solicitation of sponsors of workshops and symposia at the Annual Meeting, (6) soliciting exhibits for the Annual Meeting, and (7) improving communication between the private sector and the Society.

3. The Finance Committee. The Finance Committee shall be composed of the Treasurer (as Chair), the Chair of the Development Committee, and the President-Elect. The administrative officer of the Society may serve as an ex-officio member of this Committee. The Committee shall prepare an annual Society budget and submit it for Council approval at the time of the Annual Meeting and prior to the start of the fiscal year. This budget shall include estimates of all income sources, and appropriate estimates of expenditures for Committees, Officers, Meetings, and a Publications Operating Fund may be established upon Council approval. The Finance Committee shall consider and attempt to devise ways to increase the Society's income.

4. International Relations Committee. The International Relations Committee shall be composed of three members elected by Council from among four nominees submitted by the President. Their terms of office shall be for three years, one being elected each year. The President shall designate one member of the Committee to serve as Chair. Members of this Committee shall be the official delegates to any International Meeting and be responsible for the foreign activities of the Society.

5. Membership Committee. The Membership Committee shall be composed of three members, each serving a term of three years. The primary purposes of the Committee are to increase individual memberships in the Society and to review applications for membership. Applicants may be granted membership by the Committee. Applications must attain an approval vote of at least two-thirds of the Committee.

6. Nominating Committee. The Nominating Committee shall be composed of the immediate Past-President who will be Chair of the Committee and at least three other members of Council appointed by the President, each serving three years. Committee members may not currently be from the same institution. The Nominating Committee shall submit nominations of the offices of President-Elect, Secretary, and Treasurer. They shall also submit the names of at least two members of the Society as candidates for each position of Councilor and two members for each position on the Scientific Program Committee. It will be the responsibility of the Nominating Committee to prepare lists of nominees from the members as described in Article VII of the Bylaws and to ascertain the willingness of each nominee, if elected, to serve. The Committee transmits nominations to the Secretary for publication at least six months prior to the Annual Meeting. Other names may be added to the Ballot upon

petition in accordance with the procedures published in Article VII of the Bylaws. At least 3 months before the Annual Meeting, a Ballot containing the list of all nominees will be sent to the membership. For a member to be eligible for nomination for elective office, he/she must be an active member in good standing for a minimum of two years.

7. Publications Committee. The Publications Committee shall be composed of four members appointed by the President, each serving four years, one being appointed each year. The senior member will be the Chair. The Society Editor serves in a non-voting capacity. The Committee formulates general policy concerning all publications and makes decisions concerning publications arising out of Annual and International Meetings, subject to review and approval by the Council. The Committee is responsible for nominating an Editor(s) for Council approval. The Committee serves as a liaison between the membership and the Journal, offering advice and comment on general publication policy.

8. Rules Committee. The Rules Committee shall be composed of one member appointed each year by the President who will serve as Chair. The Chair may appoint additional members as needed. The Chair of this Committee shall serve for a term of one year and may be reappointed. The Chair of the Committee becomes the Parliamentarian of the Society with such duties as may be set forth in the Bylaws or Rules of the Society. Questions relative to the interpretation of the Constitution shall be presented to the Rules Committee. The duties of this Committee shall be to provide information for the Council on matters relating to the Constitution of the Society, its Bylaws, and acts of the Annual Meeting; to interpret for the Council the Constitution, Bylaws, and acts of the Annual Meeting; to recommend to the Council the requirements for, and privileges and obligations of, the several classes of membership; and to consider from time to time, either on its own initiative or by reference from the Council or the Membership, proposed revisions of the Constitutions and Bylaws.

9. Scientific Program Committee. The Scientific Program Committee shall be composed of six members, representing the present and next two Annual Meetings, three elected members and three members appointed by the elected members. Elected members shall each serve three years, one being elected each year. Elected members shall be nominated by the Nominating Committee and these nominees should represent the scientific interests of the Society.

The Scientific Program Committee is responsible for the scientific affairs of the Society. The Committee develops the program for the Annual Meeting, including topics and contributors for major sessions and selection of proffered papers. It arranges for the program publication and receives proposals and makes recommendations to Council concerning selection and scheduling of sites for Annual Meetings. Further, the Committee is responsible for scientific programs held in cooperation with other American organizations. The Committee is required to file a formal written summary annually with the Council.

10. Laboratory Animal Issues Committee. The Laboratory Animal Issues Committee shall be composed of four appointed members, three of whom shall serve for a term of three years, one being appointed each year by the President. The Chair of this Committee shall serve for a term of one year, and may be reappointed. The purpose of this Committee is to: 1) promote the ethical and humane use of laboratory animals as required for legitimate scientific research, 2) gather and provide the

membership with current information concerning matters that could affect the Society's purpose of promoting research in shock and trauma. Such matters might include the status of pending legislation dealing with animal care or use, the activities of animal activist groups, and national efforts to foster biomedical research. 3) In collaboration with the Program Committee, sponsor appropriate programs at the annual meetings.

ARTICLE IX (Amendments)

Amendments to the Bylaws shall be initiated according to the same procedure as amendments to the Constitution, except that a majority vote at the annual business meeting shall suffice for ratification.

Membership Directory

Abel, Francis L.
Dept. Physiology
Univ. South Carolina Sch. Med.
Columbia, SC 29208
803-733-3236

Abraham, Edward
Dept. Med.
Div. Pulmonary and
Critical Care Med.
Los Angeles, CA 90024
213-825-5988

Adams, H. Richard
Dept. Biomedical Sciences
Univ. Missouri - Columbia
Col. of Vet. Med.
Columbia, MO 65211
314-882-7011

Al Tuwaijri, Ali S.
Dept. Physiology
King Saud Med. Sch.
PO Box 2925
Riyadh, Saudi Arabia 11461

Albina, Jorge E.
Dept. of Surgery
Rhode Island Hosp.
593 Eddy St.
Providence, RI 02903
401-277-4296

Alexander, J. Wesley
Dept. Surgery
Univ. Cincinnati Col. Med.
231 Bethesda
Cincinnati, OH 45267

Allen, Elizabeth J.*
Dept. Surg.-Trauma
Cook County Hosp.
1835 W. Harrison, Rm. 3241
Chicago, IL 60640
312-633-8075

Allo, Maria D.
Dept. Surgery-Osler 624
Johns Hopkins Hosp.
600 N. Wolfe St.
Baltimore, MD 21205
301-955-2690

Alteveer, Robert J.
Physiology & Biophysics
Hahnemann Univ. Sch. Med.
230 N. Broad St.
Philadelphia, PA 19102
215-448-8220

Altura, Burton M.
Dept. Physiology/Box 31
SUNY Downstate Med. Ctr.
450 Clarkson Ave.
Brooklyn, NY 11203
212-270-2616

Alverdy, John C.
Dept. Surgery
Michael Reese Hosp.
Lake Shore Drive at 31st St.
Chicago, IL 60616
312-791-4330

Amir, Shimon
Dept. Isotope Research
Weizmann Inst. Science
Rehovot, Israel

*Associate or Student Member

Angelakos, Evangelos T.
Physiol. & Biophysics
Hahnemann Med. Col./MS409
230 N. Broad St.
Philadelphia, PA 19102
212-448-8216

Antonenko, David R.
120 Labree Ave. S.
Thief River, MN 56701
218-681-8857

Applefeld, Jack J.*
Critical Care
Good Samaritan Med. Ctr.
1111 E. McDowell Rd.
Phoenix, AZ 85006
602-239-2000

Archer, Linda T.
VA Med. Ctr.
Lab Service (113)
921 N.E. 13th St.
Oklahoma City, OK 73104
405-272-9876

Arfors, Karl E.
Pharmacia
Experimental Med.-La Jolla
11099 N. Torrey Pines Rd.
La Jolla, CA 92037
619-458-9983

Asher, Eleanor F.
953 Cherokee Rd.
Louisville, KY 40204

Babbs, Charles F.
Biomed. Eng. Ctr.
Purdue Univ.
Potter Bldg.
W. Lafayette, IN 47907
317-494-2995

Badylak, Stephen F.
Biomed. Eng. Ctr.
Purdue Univ.
Potter Engineering Bldg.
W. Lafayette, IN 47907
317-494-2995

Bagby, Gregory J.
Dept. Physiology
Louisiana State Med. Ctr.
1901 Perdido
New Orleans, LA 70112
504-568-6180

Bajo, Thomas*
Critical Care
Good Samaritan Med. Ctr.
1111 E. McDowell
Phoenix, AZ 85006
602-239-2217

Baker, Carleton H.
Dept. Physiology
Univ. South Florida
Col. Med./Box 8
Tampa, FL 33612
813-974-2590

Baker, Robert J.
Dept. Surgery
Med. Ctr. of Delaware
501 W. 14th St.
Wilmington, DE 19899

Balis, John U.
Dept. Pathology/Box 11
Univ. South Florida Col. Med.
12901 N. 30th St.
Tampa, FL 33612

Ball, Howard A.
Biochemisches Institut
Albert-Ludwigs Univ.
Herman-Herder Str. 7
Freiburg 1 BR
W. Germany D-7800

Barillo, David J.*
Dept. Surg./Burn Unit
LeHigh Valley Hosp.
1217 N. 16th St.
Allentown, PA 18102
215-435-7555

Barker, Louis A.
Dept. Pharmacology
LSU Med. Ctr.
1901 Perdido St.
New Orleans, LA 70112
504-568-4740

Barrett, John A.
Trauma Office M-3241
County Hosp.
1835 W. Harrison
Chicago, IL 60612
312-633-8075

Bastiaans, Johanna C.
Dept. Pharmacology
Univ. Amsterdam/Academic Med. Ctr.
Meibergdreef 15
Amsterdam, Netherlands 1105 AZ

Baue, Arthur E.
St. Louis Univ. Med. Ctr.
3556 Caroline St.
St. Louis, MO 63104
314-577-8100

Beamer, Kathryn C.
Dept. Surgery
West Virginia Univ.
Sch. Med.
Morgantown, WV 26505
304-293-4206

Beller, Beverly K.
Laboratory
The VA Hosp. 113
921 N.E. 13th St.
Oklahoma City, OK 73104
405-272-9876

Benjamin, Ernest
Falk ICU
Mount Sinai Hosp.
1 Gustave Levy Place
New York, NY 10029
212-650-6189

Bessey, Palmer Q.
Dept. Surgery
Washington Univ. Sch. Med.
Box 8109
St. Louis, MO 63110

Biber, Bjorn
Dept. Anesthesiology
Ostra Hosp.
Gothenburg, Sweden S 41685

Bitterman, Haim*
Dept. Internal Med. B
Lady Davis Carmel Hosp.
7 Michal St.
Haifa, Israel 34362

Blackwood, James M.
Dept. Surgery/G532
New Jersey Med. Sch.
100 Bergen St.
Newark, NJ 07103
201-643-8136

Blaisdell, F. William
Dept. Surgery
Univ. California Davis
4301 X St.
Sacramento, CA 95817
916-453-3528

Blumenstock, Frank A.
Dept. Physiology
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5655

Bond, Robert F.
Dept. Physiology
Univ. South Carolina
Sch. Med.
Columbia, SC 29208
803-733-3250

Botan, Edward A.
A.P.P. Research Cardiosurgery
C.R. Bard Inc
129 Concord Rd./P.O. Box M
Billerica, MA 01821
617-663-5353

Bottoms, Gerald D.
Dept. Veterinary
Physiol. & Pharmacol.
Purdue Univ.
W. Lafayette, IN 47907
317-493-1891

Bowen, John C.
Surgical Education
Ochsner Med. Inst.
1514 Jefferson Highway
New Orleans, LA 70121
504-834-7070

Brackett, Daniel J.
Research Service (151)
V.A. Med. Ctr.
921 N.E. 13th St.
Oklahoma City, OK 73104
405-271-2108

Breslow, Michael J.*
7 Broadridge Lane
Lutherville, MD 21093
301-561-3192

Brotman, Sheldon
Dept. General Surgery
Geisinger Med. Ctr.
Danville, PA 17821
717-271-6357

Brown, Danley F.*
3911 Scarritt Ave. #1
Kansas City, MO 64123
816-483-4572

Buchman, Timothy G.*
Dept. Surgery
Johns Hopkins
600 N. Wolfe St.
Baltimore, MD 21205

Buehren, Volker*
Dept. Trauma-Surg.
Univ. Saarland
Homburg/Saar, FRG 6650

Bulkley, Gregory B.
Dept. Surgery
Johns Hopkins Univ.
600 N. Wolfe St.
Baltimore, MD 21205
301-955-8500

Burchard, Kenneth W.
Surgical Intensive Care Unit
Rhode Island Hosp.
593 Eddy St./APC 105
Providence, RI 02903
401-277-5853

Burke, John F.
Dept. Surgery
Massachusetts Gen. Hosp.
Fruit St.
Boston, MA 02114
617-726-2809

Burns, J. Robert
Critical Care Med.
Geisinger Med. Ctr.
Danville, PA 17821

Caffrey, James L.
Dept. Physiology
Texas Col. Osteopathic Med.
E.P. Bowie At Montgomery St.
Ft. Worth, TX 76107
817-735-2085

Cain, Stephen M.
Prof. Physiol. and Biophys.
Univ. Alabama, Birmingham
UAB Station, 401 VH
Birmingham, AL 35294
205-934-4471

Caldwell, Michael D.
Dept. Surgery
Rhode Island Hosp.
Providence, RI 02902

Canada, Andrew T.*
Dept. Anesthesiology
Duke Univ. Med. Ctr.
Box 3094
Durham, NC 22710
919-684-6931

Canizaro, Hana P.
Dept. Surgery
Texas Tech Univ.
Hlth. Sci. Ctr.
Lubbock, TX 79430
806-743-2259

Canizaro, Peter C.
Dept. Surgery
Texas Tech Univ. Sch. Med.
Lubbock, TX 79430

Carli, Alain
U. Cochin Port Royal
Serv. Reanim. Polyvalente
27 Rue FBG St. Jacques
Paris, France 75674

Carmona, Richard
Surgery Trauma Services
Tucson Med. Ctr./P.O. Box 42195
Tucson, AZ 85733
602-327-5461

Carrico, C. James
Dept. Surgery
RF-25
Univ. Washington
Seattle, WA 98195

Carroll, Gilbert C.
Lake Point Tower
Apt. 4301
505 North Lake Shore
Chicago, IL 60611

Carroll, Robert G.
Dept. Physiology
East Carolina Univ. Sch. Med.
Greenville, NC 27858
919-551-2768

Carvajal, Hugo F.
Dept. Pediatrics
Univ. of Texas Med. Sch.
6431 Fannin
Houston, TX 77030
713-792-5388

Casey, Kenneth F.
Dept. Neurology
FMC
Box-6072
Aurora, CO 80045

Cavanagh, Denis
Dept. Ob/Gyn. Box 18
Univ. South Florida
Med. Ctr.
Tampa, FL 33612
813-974-2088

Cerra, Frank B.
Box 42, Mayo Bldg.
Univ. Minnesota
420 Delaware St., S.E.
Minneapolis, MN 55455
612-373-7733

Chaudry, Irshad H.
Dept. Surgery
B424 Clinical Ctr.
Michigan State Univ.
East Lansing, MI 48824
517-355-3310

Chen, Hua-Cui
Dept. Pathophysiology
Hsaing-Ya Med. Col.
5 Dong Dan San Tiao
Beijing, China

Chernow, Bart
Dept. Anesthesia & Med.
Massachusetts Gen. Hosp.
32 Fruit St.
Boston, MA 02114
617-726-2858

Chiu, Ray Chu-Jeng
Dept. Surgery
Montreal Gen. Hosp.
1650 Cedar Ave.
Montreal, PQ Canada H3G1A4
514-937-6011

Cho, Eshin
Dept. Physiology
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5658

Clemens, Mark G.
Dept. Surgery (Pediatric)
Johns Hopkins Univ. Sch. Med.
600 N. Wolfe St.
CMSC 7-121
Baltimore, MD 21205
301-955-6885

Colucci, Robert D.
27 Forest Lawn Ave.
Stamford, CT 06905
212-584-1611

Cone, John B.
Dept. Surgery
Univ. Arkansas
4301 W. Markham
Little Rock, AR 72205
501-661-6173

Connell, Reid S.
Dept. Anatomy
Sch. Med.
Oregon Health Science Ctr.
Portland, OR 97201
503-225-7811

Cook, James A.
Dept. Physiology
Med. Univ. South Carolina
171 Ashley Ave.
Charleston, SC 29425
803-792-2978

Coran, Arnold G.
Pediatric Surgery
Univ. Michigan
Mott Children's Hosp.
Ann Arbor, MI 48109
313-764-4151

Cornell, Robert P.
Div. Science
Northeast Missouri State Univ.
Kirksville, MO 63501

Corum, T.R.
MSL Unit
Upjohn International Inc.
7000 Portage Rd.
Kalamazoo, MI 49001

Cowley, R. Adams
Maryland Inst. for EMS
Univ. Maryland
22 S. Greene St.
Baltimore, MD 21201

Cronen, Paul
703-A Green Rd.
Madison, IN 47250
812-273-1591

Cryer, Henry M.
Dept. Surgery
Univ. Louisville
550 S. Jackson St.
Louisville, KY 40292
502-588-5675

Dahn, Michael S.
Univ. Health Ctr./6C
4201 St. Antoine
Detroit, MI 48201
313-577-5001

Dawidson, Ingemar J.A.
Dept. Surgery
Univ. Texas Southwestern Med. Ctr.
5323 Harry Hines Blvd.
Dallas, TX 75235
214-688-2393

Dehring, Deborah J.
Dept. Anesthesiology
Univ. Texas Med. Branch
E91
Galveston, TX 77550
409-761-1221

Demetriou, Achilles
Dept. Surgery
Vanderbilt Univ.
T-2119 Med. Ctr. North
Nashville, TN 37232
615-322-2242

Demling, Robert H.
Longwood Area
Trauma Ctr.
75 Francis Ctr.
Boston, MA 02115
617-732-7715

Doran, Jan Eva
Univ. Dept. Experimental Surgery
Inselspital
P.O. Box 10
Berne, Switzerland CH-3010

Dulchavsky, Scott A.
Dept. Surgery
SUNY at Stonybrook
Health Sci. Ctr. T19060
Stonybrook, NY 11794
516-444-1045

Dunham, C. Michael
Dept. Traumatology
MIEMSS-Univ. Maryland
22 S. Greene St.
Baltimore, MD 21201
301-528-3055

Durkot, Michael John
Dept. of the Army
USARIEM
Heat Research Div.
Natick, MA 01760

Dutton, Robert
21 Pinedale Ave.
Delmar, NY 12054

Ebata, Toshiaki
Dept. Surgery
Sapporo Med. Col.
S-1, W-16, Chuo-Ku
Sapporo, Japan 060

Emerson, Thomas E.
Dept. Physiology
Cutter Group of Miles Labs Inc.
Fourth & Parker St./Bld28A
Berkeley, Ca 94710
415-420-5414

Enderson, Blaine L.
Dept. Surgery
Univ. Tennessee Med. Ctr.
1924 Alcoa Highway
Knoxville, TN 37920

Engquist, Allan
Dept. Int. Care Therapy
Bispebjerg Hosp.
Copenhagen, Denmark 2400

Ephgrave, Kimberly S.
Dept. Surgery
Univ. Iowa Col. Med.
Iowa City, IA 52240
319-338-0581

Fabian, Timothy C.
Dept. Surgery
Univ. Tennessee
956 Court Ave.
Memphis, TN 38163
901-528-5909

Fagraeus, Lennart
Dept. Anesthesiology
Christiana Hosp.
P.O. Box 6001
4755 Ogletown-Stanton Rd.
Newark, DE 19718

Fantini, Gary A.
Dept. Surgery
New York Hosp. Cornell
525 E. 68th St./Room F739
New York, NY 10021
212-472-5640

Feola, Mario
Dept. Surgery
Texas Tech. Univ.
Health Sciences Ctr.
Lubbock, TX 79430

Ferguson, James L.
Physiol. & Biophys./Rm. E 202
Univ. Illinois at Chicago
835 S. Wolcott/CMHSA M/C 901
Chicago, Il 60612
504-568-6183

Fessler, John F.
Dept. Large Animal Clinics
Sch. Veterinary Med.
Purdue Univ.
W. Lafayette, IN 47907
317-494-8548

Fettman, Martin J.
Dept. Pathology
Colorado State Univ.
Col. Veterinary Med.
Ft Collins, CO 80523
303-491-7592

Feuerstein, Giora Z.
Neurobiology Research Unit
USUHS
4301 Jones Bridge Rd.
Bethesda, MD 20814
202-295-3690

Fiddian-Green, Richard
Gen. Surgery
Univ. Mass. Med. Ctr.
55 Lake Ave.
Worcester, MA 01605
617-856-3581

Filkins, James P.
Dept. Physiology
Loyola Univ. Med. Ctr.
2160 S. First Ave.
Maywood, IL 60153
312-531-3330

Fink, Mitchell P.
Dept. Surgery
Univ. Mass. Med. Ctr.
55 Lake Ave. North
Worcester, MA 01655
617-856-3036

Fischer, Ronald P.
Dept. Surgery
Univ. Texas Med. Sch.
6431 Fannin
Houston, TX 77030
713-792-5407

Fish, Richard E.
Dept. Lab. Animal Med.
M144 Med. Sci. Bldg.
Univ. Missouri
Columbia, MO 65212
314-882-3111

Flancbaum, Louis J.
UMDNJ-Rutgers Med. Sch.
Academic Health Science Ctr.
CN19
New Brunswick, NJ 08903
201-937-7920

Fletcher, John Raymond
Dept. Surgery
St. Thomas Hosp.
4220 Harding Rd.
Nashville, TN 37202
615-386-6758

Flint, Lewis M.
Dept. Surgery
SUNY AB
462 Grider St.
Buffalo, NY 14215
716-894-1213

Flynn, John T.
Dept. Physiology
Jefferson Med. Col.
1020 Locust St.
Philadelphia, PA 19107
215-928-8825

Flynn, Timothy C.
Dept. Surgery (112)
V.A. Med. Ctr.
Gainesville, FL 32602

Foca, Alfredo
Via Reggio Campi, 45 (1 TR)
Reggio
Calabria, Italy 89100

Fortune, John B.
Dept. Surgery, A-61
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5793

Fry, Donald E.
Dept. Surgery
Univ. New Mexico Sch. Med.
2211 Lomas, N.E.
Albuquerque, NM 87131

Furste, Wesley L.
Dept. Surgery
Ohio State Univ.
3545 Olentangy River Rd.
Columbus, OH 43214
614-268-4224

Gaffin, Stephen L.
Dept. Physiology
Univ. Natal Med. Sch.
P.O. Box 17039, Congella
Durban 4013, South Africa

Gann, Donald S.
Prof. of Surgery
Univ. Maryland Sch. Med.
22 South Green St.
Baltimore, MD 21201

Garcia-Barreno, Pedro
Service Exper. Med. and Surg.
Hosp. Provincal de Madrid
c/o Dr. Esquerdo
46 Madrid-30 Spain

Garrison, Richard N.
Dept. Surgery
Univ. Louisville Sch. Med.
550 S. Jackson St.
Louisville, KY 40292
502-588-5453

Geelhoed, Glenn W.
Dept. Surgery
George Washington Univ.
2150 Pennsylvania Ave.
Washington, DC 20037
202-676-4427

Geer, Ralph T.
Dept. Anesthesia
Hosp. Univ. Pennsylvania
3400 Spruce St.
Philadelphia, PA 19104
215-662-3762

Geiser, Ronald W.
Upjohn International, Inc.
Kalamazoo, MI 49001

Gentili, David R.
Falk-ICU Dept. of Surgery
The Mount Sinai Med. Ctr.
One Gustave Levy Place
New York, NY 10029
212-650-8867

Gervin, Alfred S.
Dept. Surgery
Med. Col. Virginia
MCV Box 478-MCV Station
Richmond, VA 23298
804-786-7350

Gill, William
Critical Care Services
Northwest Texas Hosp.
P.O. Box 1110
Amarillo, TX 79175

Giovannini, Ivo
Via Alessandro VII, 45
Rome, Italy I-00167

Glenn, Thomas M.
Sr. V.P. & Dir. Research-#301
CIBA-GEIGY Corp.
556 Morris Ave.
Summit, NJ 07901
212-277-5257

Goldfarb, I. William
4815 Liberty Ave.
Suite 340
Pittsburgh, PA 15224
412-681-5786

Goldfarb, Roy D.
Dept. Physiology
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5663

Goodwin, Cleon W.
Burn Ctr.-Rm. F2314
NY Hosp.-Cornell Med. Ctr.
525 E. 68th St.
New York, NY 10021

Goto, Masakatsu
Dept. Pediatrics
Loyola Univ. Stritch Sch. Med.
2160 S. First Ave.
Maywood, IL 60153
312-531-3372

Gould, Steven A.
Dept. Surgery
Michael Reese Hosp.
Lake Shore Dr. at 31st St.
Chicago, IL 60616
312-791-5593

Greenburg, A. Gerson
Surgery
The Miriam Hosp.
164 Summit Ave.
Providence, RI 02906
401-274-3700

Greenfield, Lazar J.
Univ. Michigan
2101 Taubman Health Care Ctr.
Ann Arbor, MI 48109

Grenvik, Ake
Critical Care Med./Rm 2413
Presbyterian Univ. Hosp.
Desoto & Ohara St.
Pittsburgh, PA 15213

Griffin, Andrew J.
Dept. Pediatrics
Illinois Masonic Med. Ctr.
836 W. Wellington Ave.
Chicago, IL 60657
312-883-7147

Grindlinger, Gene A.
Div. Surgery
Boston City Hosp.
Peabody 1/818 Harrison St.
Boston, MA 02118
617-424-5224

Groff, Diller B.
Dept. Surgery
Univ. Louisville
Children's Hosp.
Louisville, KY 40232

Gross, Ditza
Respiratory ICU & Exper. Surgery
Hadassah Univ. Hosp.
Kiryat Hadassah POB 12000
Jerusalem, Israel 91120

Guice, Karen S.
Dept. Surgery
Univ. Michigan
Box 0331 Taubman Hlth. Care Ctr.
Ann Arbor, MI 48109
313-763-5746

Gumbs, Milton A.
The Bronx Lebanon Hosp. Ctr.
1650 Grand Concourse
Bronx, NY 10457
212-588-7000

Gunther, Robert A.
Dept. Surgery
Sch. Med.
4301 X St.
Sacramento, CA 95817

Gurll, Nelson J.
Dept. Surgery
Univ. Iowa Col. Med.
Iowa City, IA 52242
319-356-1794

Haddy, Francis J.
Dept. Physiology
Uniformed Serv. U. Hlth. Sci.
4301 Jones Bridge Rd.
Bethesda, MD 20014
202-295-2160

Haglind, Eva
Dept. Surgery I
Univ. Goteborg
Sahlgren's Hosp.
Goteburg, Sweden S-41345

Haglund, Ulf
Dept. Surgery
Uppsala Univ. Hosp.
Uppsala, Sweden
46-18-66

Halevy, Simon
Anesthesiology
Nassau County Med. Ctr.
East Meadow, NY 11554
516-542-2256

Haljamae, Hengo
Dept. Anesthesiology
Sahlgren's Hosp.
Univ. Goteborg
Goteborg, Sweden S-41345

Hall, Edward L.*
900 Gordon Ave.
Thomasville, GA 31792

Hall, John R.
Dept. Pediatric Surgery
Cook County Children's Hosp.
Room B-40/700 South Wood St.
Chicago, IL 60612
312-633-8554

Halpern, Neil A.*
Dept. Surgery Anesthesia
Bronx V.A. Med. Ctr.
130 W. Kingsbridge Rd.
Bronx, NY 10468

Halushka, Perry V.
Dept. Pharmacology
Med. Univ. S. Carolina
171 Ashley Ave.
Charleston, SC 29425
803-792-2471

Hamar, Janos
Exp. Research Lab.
Nat. Inst. Traumatology
Mezo Imre UT 17
1081 Budapest, Hungary

Hamburger, Steven A.
Oklahoma Med. Res. Foundation
Molecular Toxicology Res. Group
825 N.E. 13th St.
Oklahoma City, OK 73104
405-271-7425

Harkema, James M.
Dept. Surgery
Michigan State Univ.
B4112 Clinical Ctr.
East Lansing, MI 48824

Harlan, John M.
Dept. Med. Hematology
Univ. Washington
325 Ninth Ave. ZA-34
Seattle, WA 98104
206-223-3157

Harmon, John W.
Chief Surgical Service
Washington VA Med. Ctr.
Washington, D.C. 20422

Harris, Patrick D.
Dept. Physiology and Biophysics
Univ. Louisville
Health Sciences Ctr. A-1115
Louisville, KY 40292
502-588-5371

Harrison, Marvin W.
Div. Pediatric Surgery
Oregon Health Sciences Univ.
3181 S.W. Sam Jackson Park Rd.
Portland, OR 97201

Haupt, Marilyn T.
Internal Med.
Wayne State Univ.
4201 St. Antoine
Detroit, MI 48201
313-494-3265

Hauptman, Joe
Small Animal Clinical Sciences
Michigan State Univ.
Veterinary Clinical Ctr.
East Lansing, MI 48824
517-355-6570

Hayasaka, Hiroshi
Sapporo Med. Col.
S-1, W-16
Sapporo
Hokkaido, Japan

Hedlund, Bo E.*
Biomed. Frontiers, Inc.
1095 10th Ave. S.E.
Minneapolis, MN 55414
612-378-0228

Helling, Thomas S.*
4320 Wornall
Suite 308
Kansas City, MO 64111
816-753-7460

Herman, Clifford M.
Dept. Surgery ZA-16
Harborview Med. Ctr.
325 9th Ave.
Seattle, WA 98104
206-223-3064

Herndon, David N.
Shriners Burns Inst.
610 Texas Ave.
Galveston, TX 77550
409-761-2454

Herron, David K.
Dept. Medicinal Chem.
Lilly Research Labs
Lilly Corp. Ctr.
Indianapolis, IN 46285
317-276-4670

Hess, Michael L.
Dept. Physiology & Med.
Med. Col. Virginia
Box 281 MCV Station
Richmond, VA 23298
804-786-6345

Hill, Molly R.
Microbiology and Immunology
Oklahoma Univ. Hlth. Sci. Ctr.
P.O. Box 26901
Oklahoma City, OK 73190

Hinshaw, Daniel B.
Dept. Surgery (112)
V.A. Hosp.
2215 Fuller Rd.
Ann Arbor, MI 48105
313-761-7658

Hinshaw, Lerner B.
Oklahoma Med. Research Fndn.
825 N.E. 13th St.
Oklahoma City, OK 73104
405-271-7890

Hirasawa, Hiroyuki
Dept. Emerg. & Crit. Care Med.
Chiba Univ. Sch. Med.
1-8-1 Inohana
Chiba, Japan

Hitner, Henry W.
Dept. Pharmacology
Phila. Col. Osteopathic Med.
4150 City Ave.
Philadelphia, PA 19131
215-581-6600

Hock, Carl E.*
UMDNJ-SOM
Dept. Med./Research Div.
401 Haddon Ave.
Camden, NJ 08103
609-757-7782

Hoffman, James P.
Prof. Communications
Merck Sharp & Dohme
West Point, PA 19486
215-699-5311

Holaday, John W.
Med. Neurosciences
Div. Neuropsychiatry
WRAIR/WRAMC
Washington, D.C. 20307
202-576-3028

Holcroft, James W.
Dept. Surgery
Univ. California, Davis
4301 X St./R 257
Sacramento, CA 95817

Horpacsy, Geza
Inst. Experimental Med.
Univ. Cologne
Robert-Koch St. 10
Koln 41, West Germany D-5000

Horton, Jureta
Dept. Surgery
Univ. Texas Health Sci. Ctr.
5323 Harry Hines
Dallas, TX 75235

Houtchens, Bruce A.
Dept. Surgery
UTHSCH/Suite 4274
6431 Fannin
Houston, TX 77030

Hubbard, Joel D.*
Sch. of Life & Health Sci.
Univ. Delaware
Newark, DE 19716
806-765-8190

Iberti, Thomas J.
Falk Intensive Care Unit
Mount Sinai Hosp.
1 East 100 St.
New York, NY 10029
212-650-6188

Imai, Takasuke
Intensive Care Unit
Gunma Univ. Sch. of Med.
3-39 Showa-Machi
Maebashi 371, Japan

Ishida, Kimiko
Stanford Univ. Med. Ctr.
R-317
Stanford, CA 94305
415-725-6507

Jabs, Clarence M.
Dept. Surgery
Kuwait Univ. Fac. Med.
PO Box 24923
Safat, Kuwait 13110

Jacobs, Donald M.*
Dept. Surgery
Hennepin County Med. Ctr.
701 Park Ave.
Minneapolis, MN 55415

Jain, Krishna M.
Advanced Vascular Surgery
Suite 110
1535 Gull Rd.
Kalamazoo, MI 49001

James, Paul M., Jr.
Emergency Med. Services
176 Oakmont Rd.
Wheeling, WV 26003
304-242-1111

Janssen, Herbert F.
Dept. Orthopaedic Surgery
Texas Tech. Univ.
Health Sci. Ctr.
Lubbock, TX 79430

Jin, Huiming
Dept. Pathophysiology
Shanghai Med. Univ.
138 Yi Xue Yuan Rd.
Shanghai, China 200032

Johnson, Martha A.*
Vet. Physiology & Pharm.
Purdue Univ.
Lynn Hall-Sch. of Vet. Med.
W. Lafayette, IN 47907
312-494-8640

Johnson, Gerald III
Dept. Physiology
Jefferson Med. Col.
1020 Locust St.
Philadelphia, PA 19107
215-928-7627

Jones, Stephen
Dept. Physiology
Loyola Univ. of Chicago
Sch. Med.
2160 S. First Ave.
Maywood, IL 60153
312-531-3297

Joyce, Harry H.
2819 Coachlite
Portage, MI 49081

Jurkovich, Gregory J.
Dept. Surgery
Harborview Med. Ctr.
325 9th Ave. ZA-16
Seattle, WA 98104
206-223-5912

Kamiyama, Yasuo
First Dept. Surgery
Kyoto Univ. Faculty Med.
54-Kawara-Cho, Shogoin, Sakyo-ku
Kyoto, Japan 606

Kaplan, John E.
Dept. Physiology
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5543

Karlstad, Michael D.
Dept. Anesthesiology
Univ. Tenn. Med. Ctr.
1924 Alcoa Hwy.
Knoxville, TN 37920
615-544-9220

Kelly, Kathleen M.*
936 Summit Ave.
River Edge, NJ 07661
201-441-2255

Keppler, Dietrich
Biochemistry Med. Sch.
Albert Ludwigs Univ.
Hermann-Herder-Str. 7
Freiburg, West Germany D-7800

Kerstein, Morris D.
Dept. Surgery
Tulane Med. Sch.
1430 Tulane Ave.
New Orleans, LA 70112
312-791-5595

Kilpatrick, Laurie
Div. Allergy & Immunology
Children's Hosp. Phil.
34th St. and Civic Center Blvd.
Philadelphia, PA 19104
215-596-8750

Klein, Diane M.
Dept. Physiology
Loyola Univ. Med. Ctr.
2160 S. First Ave.
Maywood, IL 60153

Kline, Mark W.
Dept. Pediatrics
St. Louis Univ.
1465 S. Grand Blvd.
St. Louis, MO 63104
314-577-5644

Kober, Philip M.
2009 Harrison St.
Evanston, IL 60201

Kohler, John P.
1506 Youngs Ford Rd.
Gladwyne, PA 19035

Kovach, Aristztid G.B.
Experimental Res. Dept. Physiol.
Semmelweis Med. Univ.
Vloi UT 78A
Budapest, Hungary 1082

Koyama, Shozo
Dept. Physiology
Shinshu Univ. Sch. Med.
3-1-1 Ashai, Matsumoto
Nagano, Japan 390

Kramer, George C.
Dept. Human Physiology
Sch. Med.
Univ. California, Davis
Davis, CA 95616
916-752-6226

Krausz, Michael M.
Dept. Surgery B
Hadassah Univ. Hosp.
Jerusalem, Israel 91120

Kreis, David J.
Chief of Trauma
Health Sci. Ctr. (T19,020)
SUNY-Stony Brook
Stony Brook, NY 11794
516-444-2018

Kudsk, Kenneth A.
Surgery/Rm E228 Coleman Bldg.
Univ. Physicians Fndn., Inc.
956 Court Ave.
Memphis, TN 38163

Kutsky, Phyllis B.
Dept. Physiology
Texas Col. Osteopathic Med.
Camp Bowie at Montgomery
Fort Worth, TX 76107
817-735-2083

Lamonica Groves, Concetta R.
Admitting Area/MIEMSS
Univ. Maryland
22 S. Greene St.
Baltimore, MD 21201

Lang, Charles
Dept. Physiology
LSUMC
1901 Perdido St.
New Orleans, LA 70112
504-568-4394

Langdale, Lorrie A.
Surgical Service (112)
V.A. Med. Ctr.
1660 S. Columbian Way
Seattle, WA 98108
206-764-2255

Lanza-Jacoby, Susan
Dept. Surgery
Jefferson Med. Col.
1025 Locust St.
Philadelphia, PA 19107
215-928-7903

Ledgerwood, Anna M.
Detroit Receiving Hosp.
Univ. Health Ctr.
4201 St. Antoine
Detroit, MI 48201
313-494-3485

Lee, Bing C.
214 Lancaster Dr.
Piscataway, NJ 07054
518-445-3125

Lefer, Allan M.
Dept. Physiology
Jefferson Med. Col.
1020 Locust St.
Philadelphia, PA 19107
215-928-7760

Leibowitz, David A.*
99-66 65th Ave.
Forest Hills, NY 11374
718-830-0918

Levenson, Stanley M.
Yeshiva Univ.
Albert Einstein Col. Med.
1300 Morris Park/Rm 740 Forsch.
Bronx, NY 10461
212-430-2273

Levy, Jerrold H.
Dept. Anesthesiology
Emory Hosp.
1364 Clifton Rd. N.E.
Atlanta, GA 30322
404-321-0111

Lewis, David H.
Grangatan 7
Linkoping, Sweden S-58245

Lewis, Frank R.
Dept. Surgery
San Francisco Gen. Hosp.
1001 Potrero Ave./Ward 3A25
San Francisco, CA 94110
415-821-8818

Ligas, James R.
Dept. Surgery
St. Francis Hosp. & Med. Ctr.
114 Woodland St.
Hartford, CT 06105

Little, Roderick A.
Med. Res. Council Trauma Unit
Univ. Manchester
Oxford Rd.
Manchester, UK MI39PT

Liu, Maw-Shung
Dept. Physiology
St. Louis Univ. Sch. Med.
1402 S. Grand Blvd.
St. Louis, MO 63104
314-577-8244

Lobe, Thom E.
Dept. Surgery
956 Court Ave.
Suite G212
Memphis, TN 38163

Loegering, Daniel J.
Dept. Physiology/Room MS 355
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5662

Longnecker, David E.
Dept. Anesthesiology
Univ. Virginia Med. Ctr.
P.O. Box 238
Charlottesville, VA 22908
804-924-2283

Lorenz, Wilfried
Dept. Theoretical Surg.
Univ. Marburg
Klinikum Laawberge
355 Marburg, FRG
011-496-4212

Lucas, Charles E.
Dept. Surgery
Wayne State Univ.
540 E. Canfield
Detroit, MI 48201
313-494-3486

Luebbe, Andreas S.*
Dept. Physiology & Biophysics
Univ. Louisville
HSC A1115
Louisville, KY 40206
502-588-5371

Lundberg, Dag
Dept. Anesthesiology
Med. Ctr.
Durham, NC 27710

Lundsgaard-Hansen, P.
Dept. Experimental Surgery
Inselspital
P.O. Box 10
Berne, Switzerland CH3010

Luo, Zheng Yao
Dept. Pathophysiology
Hunan Med. Col.
Changsha Hunan
Hunan, China

Lust, Robert M.
Div. Cardiac Surg.
E. Carolina Med. Ctr.
Greenville, NC 27858

Lutherer, Lorenz O.
Dept. Physiology
Texas Tech. Univ.
Health Science Ctr.
Lubbock, TX 79430

Machiedo, George W.
UMDNJ
New Jersey Med. Sch.
100 Bergen St.
Newark, NJ 07103
201-763-8431

Maier, Ronald V.
Dept. Surgery ZA-16
Harborview Med. Ctr.
Univ. Washington
Seattle, WA 98104
206-223-4732

Majerus, Thomas C.
7285 Monon Ct.
Indianapolis, IN 46256

Maksad, Ali K.
91 Bayview Ave.
E. Providence, RI 02915

Malangoni, Mark A.
Dept. Surgery
Univ. Louisville
550 S. Jackson St.
Louisville, KY 40292
502-588-5413

Malcolm, Diana S.
Dept. Surgery
Uniformed Serv. Univ.
4301 Jones Bridge Rd.
Bethesda, MD 20814
202-295-3707

Markov, Angel K.
2500 North State St.
Jackson, MS 39216

Marshall, Bryan E.
Dept. Anesthesiology
Hosp. Univ. Pennsylvania
3400 Spruce St.
Philadelphia, PA 19104
215-662-3766

Marshall, Carol
Dept. Anesthesiology
Univ. Pennsylvania
3400 Spruce St.
Philadelphia, PA 19104

Marshall, Lawrence F.
Surgery Neurosurg/H893
Univ. Calif. San Diego Med. Ctr.
225 Dickinson St.
San Diego, CA 92103
714-294-5542

Martin, Louis F.
Dept. Surgery
Milton S. Hershey Med. Ctr.
Penn State Univ./P.O. Box 850
Hershey, PA 17033

Martyn, Jeevendra
Dept. Anesthesia
Massachusetts Gen. Hosp.
Boston, MA 02114
617-726-8807

Marzella, Louis
Dept. Pathology and MIEMSS
Univ. Maryland
10 S. Pine St.
Baltimore, MD 21201
301-528-3223

Massion, Walter H.**
4700 Willard Ave.
Oklahoma City, OK 73105

Matera, Giovanni
Via de Nava 4
89100 Reggio
Calabria, Italy

Matson, James R.*
7777 Forest Lane
Bldg. A, Floor 12
Dallas, TX 75230

McArdle, A. Hope
Univ. Surgical Clinic
Montreal Gen. Hosp.
1650 Cedar Ave.
Montreal, PQ, Canada H3G1A4
514-937-8951

McCallum, R.E.
Microbiology and Immunology
Univ. Oklahoma Health Sci. Ctr.
P.O. Box 26901
Oklahoma City, OK 73190
405-271-2133

McConn, Rita
40 S. Broadway
Irvington-on-Hudson
New York, NY 10533

McCoy, Sue
Box 265
Mountain Home, TN 37684

McCuskey, Robert S.
Dept. Anatomy
Univ. Arizona
Health Sci. Ctr.
Tucson, AZ 85724
602-626-6084

**Emeritus Member

McDonough, Kathleen H.
Dept. Physiology
Louisiana State Univ. Med. Ctr.
1901 Perdido St.
New Orleans, LA 70112
504-568-6171

McIntosh, Tracy K.
Dept. Surgery
Univ. Connecticut Hlth. Ctr.
Surgery Res. Ctr., Rm L-1096
Farmington, CT 06032
203-679-4617

McNamara, J. Judson
Dept. Surgery
Univ. Hawaii Sch. Med.
1301 Punchbowl St.
Honolulu, HI 96813
808-547-4253

McSwain, Norman E.
Dept. Surgery
Tulane Univ. Med. Ctr.
1430 Tulane Ave.
New Orleans, LA 70112

Mela-Riker, Leena M.
Dept. Surgery
Oregon Hlth. Sci. Univ.
Sch. Med.
Portland, OR 97201
503-225-7805

Meng, Xian Jun
Inst. Basic Med. Sci. Res.
Gen. Hosp. PLA
28 Fu Xing Rd.
Beijing, China 100853

Meredith, Jay W.
Dept. Surgery
Bowman Gray Sch. Med.
300 S. Hawthorne Rd.
Winston-Salem, NC 27103
919-748-4547

Mihm, Frederick
Dept. Anesthesia
Stanford Univ. Sch. Med.
Room S 278
Stanford, CA 94305
415-723-6415

Militello, Philip
MIEMSS
Univ. Maryland
22 S. Greene St.
Baltimore, MD 21201

Miller, Harvey I.
Dept. Physiology
Louisiana State Med. Ctr.
1542 Tulane Ave.
New Orleans, LA 70112
504-568-6177

Moore, Ernest E.
Dept. Surgery
Denver Gen. Hosp.
777 Bannock St.
Denver, CO 80204
303-893-7045

Moore, James N.
Dept. Large Animal Med.
Col. Veterinary Med.
Univ. Georgia
Athens, GA 30602
404-542-6324

Morgan, Anthony S.
St. Francis Hosp. and Med. Ctr.
114 Woodlawn St.
Hartford, CT 06105
203-548-4255

Morita, Shigeho
Dept. Anesthesia
Teikyo Univ.
3426-3 Anegasaki/Ichihara-City
Chiba, Japan 29901

Morris, Debra D.
Large Animal Med.
Univ. Georgia
Col.Vet. Med.
Athens, GA 30602
404-542-6368

Moss, Gerald
Biomed. Engineering
Rensselaer Polytech. Inst.
Troy, NY 12181
518-270-6573

Moss, Gerald S.
Dept. Surgery
Michael Reese Hosp.
29th St./Ellis Ave.
Chicago, IL 60616
312-791-2862

Mouton, Wynand L.
Dept. Med. Biochemistry
P.O. Box 63
Tygerberg, South Africa 7505

Mulder, David S.
Dept. Surgery
Montreal Gen. Hosp.
Room 633
Montreal, Que, Canada H3G 1A4
514-935-4888

Mullins, Richard J.
Dept. Surgery
Univ. Louisville
530 S. Jackson St.
Louisville, KY 40202
502-588-5453

Myrvold, Helge E.
Univ. Trondheim
Surgery/Regionsykehuset
I Trondheim
Trondheim, Norway 7000

Nagler, Arnold
Pre Clinical Med. Educ.
NY Col. Osteopathic Med.
P.O. Box 170 Wheatly
Old Westbury, NY 11568
212-430-2266

Nance, Francis C.
Dept. Surgery
St. Barnabas Med. Ctr.
Old Short Hills Rd.
Livingston, NJ 07039
504-568-4756

Naylor, Jonathan M.
Dept. Vet. Clinical Studies
Univ. Saskatchewan
Saskatoon
Saskatchewan, Canada S7N 0W0
306-343-4521

Neiberger, Richard E.
1302 N.W. 30 St.
Gainesville, FL 32605

Nelson, Karl M.
Dept. Research
Baptist Med. Ctrs.-Princeton
701 Princeton Ave.
Birmingham, AL 35211
205-783-3220

Nelson, Loren D.
218 Med. Ctr. South
2100 Pierce Ave.
Nashville, TN 37212

Nelson, Robert M.
Chairman, Dept. Surgery
Meridia Huron Hosp.
13951 Terrace Rd.
Cleveland, OH 44112

Nelson, William R.
Trauma Program
Sunnybrook Med. Ctr./Univ. Toronto
2075 Bayview/Room 4978 H Wing
Toronto, Canada M4N 3M5
416-486-3290

Nemoto, Edwin M.
Dept. Anesthesiology
Univ. Pittsburgh
1081 Scaife Hall
Pittsburgh, PA 15261
412-648-9869

Neugebauer, Edmund
Ctr. Operative Med. 1
Inst. Theoretical Surg.
Philipps Univ.
Baldinger Str.
Marburg, FRG D-3550

Novelli, Gian Paolo
Policlinico Di Caregi
Inst. Anesthesiology and
Intensive Care
Florence, Italy 50134

O'Benar, John D.
Military Trauma Research
Letterman Army Inst. Rsch.
Presidio of San Francisco
San Francisco, CA 94129
415-561-3385

Ochoa, Ricardo
Unit 7263-209-2
The Upjohn Co.
Portage, MI 49001

Oei, Howard
Neurosci./Cardiovasc. Res.
CIBA-GEIGY Pharmaceutical Div.
556 Morris Ave.
Summit, NJ 07901
201-277-5202

Oestern, Hans-Jorg
Unfallchirurg Abteilung
Allgemeines Krankenhaus Celle
Siememsplatz 4
Celle, West Germany 3100

Ogata, Hiromaru
Dept. Anesthesiology
Dokkyo Univ. Sch. Med.
880 Mibu Shimotsuga Gun
Tochigi Pref, Japan 321-02

Ogawa, Ryo
Dept. Anesthesiology
Nippon Med. Sch.
Sendagi 1-1-5, Bunkyo-ku
Tokyo, Japan 113

Ohkawa, Masanori
Dept. Crit. Care Med.
Chiba Univ. Sch. Med.
1-8-1, Inohana, Chiba
Chiba 280, Japan

Ohtake, Yoshio
Emerg. and Crit. Care Med.
Chiba Univ. Sch. Med.
1-8-1 Inohana
Chiba, Japan

Okabe, Eiichiro
Pharmacology
Kanagawa Dental Col.
82-Inaokacho/238 Yokosuka
Kanagawa, Japan

Okada, Kazuo
Dept. Anesthesiology
Teikyo Univ.
2-11-1 Kaga Itabashi-ku
Tokyo, Japan 173

Okuda, Minoru
Hatudai 1-49-3-301
Shibuya-Ku
Tokyo 151, Japan

Oldham, Keith
Sect. Pediatric Surgery
Room F7916/Mott Children's Hosp.
Univ. Michigan
Ann Arbor, MI 48109

Omann, Geneva M.
Dept. Gen. Surg. Res. SVC151
Univ. Michigan
2215 Fuller Rd.
Ann Arbor, MI 48105
313-769-7100

Panacek, Edward A.
Dept. Critical Care
2074 Abington Rd.
Cleveland, OH 44106

Papadakos, Peter J.*
Surg. ICU, Dept. Anesthesiol.
Box 604
Univ. Rochester
601 Elmwood Ave.
Rochester, NY 14642
716-275-2141

Parker, Janet L.
Dalton Research Ctr.
Research Park
Univ. Missouri
Columbia, MO 65211
314-882-7274

Parratt, James R.
Dept. Physiology & Pharmacology
Univ. Strathclyde Royal Col.
204 George St.
Glasgow, Scotland G1 1XW

Passmore, John C.
Physiology and Biophysics
Univ. Louisville Sch. Med.
Louisville, KY 40292
502-588-5382

Pate, James W.
Dept. Surgery
Univ. Tennessee
956 Court Ave.
Memphis, TN 38163
901-528-5912

Patterson, C. Richard
Univ. Physicians Fndn.
956 Court Ave.
Suite G 218
Memphis, TN 38163
901-528-5715

Paxson, Charles L.
1934 130 Lane
Coonrapids, MN 55433

Pearce, Frederick J.
Dept. Surgery
Univ. Rochester Sch. Med.
575 Elmwood Ave.
Rochester, NY 14642
716-275-7820

Peitzman, Andrew P.
Dept. Surgery
Univ. Pittsburgh Sch. Med.
1087 Sciafe Hall
Pittsburgh, PA 15261

Phillips, Robert W.
Physiology and Biophysics
Colorado State Univ.
Fort Collins, CO 80523

Pinsky, Michael R.
Dept.Anesthesiology
Univ. Pittsburgh
3550 Terrace St.
Pittsburgh, PA 15261
412-648-9613

Pivon, Richard J.
Experimental Surgery
McGill Univ.
740 Dr. Penfield Ave.
Montreal, Que, Canada H3A 1A4
514-398-3982

Plemmons, Bob C.
Professional Communications
Upjohn International Inc.
7000 Portage Rd.
Kalamazoo, MI 49001
616-323-4371

Pohlman, Timothy H.
Dept. Surgery, RF-25
Univ. Washington
Seattle WA 98192
206-543-6273

Poole, Galen
1664 Twining Dr.
Rantoul, IL 61866
217-495-3205

Procter, Charles D.
Dept. Pharmacol.
Div. Basic Science
Mercer Univ. Med. Sch.
1550 College St.
Macon, GA 31207

Proctor, Herbert J.
Dept. Surgery
Univ. North Carolina
at Chapel Hill
Chapel Hill, NC 27514
919-966-4389

Pruitt, Basil A., Jr
U.S. Army Inst. Surgical Research
Ft. Sam Houston, TX 78234
512-221-2720

Pryor, Robert W.*
7777 Forest Lane
Bldg. A, Floor 12
Dallas, TX 75230

Rackow, Eric C.
Dept. Medicine
Chicago Med. Sch.
3333 Green Bay Rd.
North Chicago, IL 60064
312-583-3291

Ransom, Kenneth J.
Trauma Service
St. Masry Med. Ctr.
1050 Linden Ave/Box 887
Long Beach, CA 90801
913-588-6124

Rao, Papineni
Ob/Gyn Box 18
Univ. South Florida Col. Med.
12901 N. 30th St.
Tampa, FL 33612
813-974-2088

Raymond, Richard M.
Cerebral Blood Flow Lab.
Loyola Univ. Med. Ctr.
2160 S. First Ave.
Maywood, IL 60153

Reed, R. Lawrence
Dept. Surgery
Univ. Texas Med. Sch., Houston
6431 Fannin, Texas Med. Ctr.
Houston, TX 77030
713-792-5407

Reese, Andy C.
Cell & Molecular Biology
Med. Col. Georgia
1120 15th St.
Augusta, GA 30912
404-828-3757

Reichard, Sherwood M.
Div. Radiobiology
Med. Col. Georgia
1120 15th St.
Augusta, GA 30912
404-721-2601

Reines, H. David
Anesthesiology Surgery
Med. Univ. South Carolina
171 Ashley Ave.
Charleston, SC 29425
803-792-2346

Reynolds, David G.
Dept. Surgery
Univ. South Florida
Tampa, FL 33612
813-974-2411

Rhodes, Robert S.
Dept. Surgery
Univ. Misssissippi Sch. Med.
2500 N. State St.
Jackson, MS 39216-4505

Rice, Charles L.
Dept. Surgery
Harborview Med. Ctr.
325 Ninth St., ZA-16
Seattle, WA 98104
206-223-3563

Rickert, William B.**
224 Yam Gandy Rd.
Savannah, GA 31411
912-598-0266

Rink, Richard D.
Dept. Anatomy
Univ. Louisville Health Sci. Ctr.
Louisville, KY 40292
502-588-5180

Risberg, Bo I.
Dept. Surgery I
Univ. Goteborg
Sahlgren's Hosp.
Goteborg, Sweden S-41345

Rocha-e-Silva, Mauricio
Research Div.
Instituto do Coracao
Av Eneas Carvalhd Aguiar 44
São Paulo, Brazil 05403

Rodning, Charles B.
2451 Fillingim St.
Mobile, AL 36617
205-471-7034

Rogers, Charles E.
Dept. Surgery
St. Francis Hosp.
100 Port Washington Blvd.
Roslyn, NY 11576
516-627-8777

Romanosky, Albert J.
Dept. Medicine
Univ. Maryland Hosp.
22 S. Greene St.
Baltimore, MD 21201

Rosen, Arthur L.
Dept. Surgery
Michael Reese Hosp.
Lake Shore Dr. at 31st St.
Chicago, IL 60616
312-791-5580

Roth, Bryan L.
Surg. Research Branch
Naval Med. Res. Inst.
Bethesda, MD 20814
202-295-2406

Rowe, Marc I.
Dept. Surgery
Children's Hosp.
3705 Fifth Ave. at Desoto
Pittsburgh, PA 15213
412-647-5050

Rush, Benjamin F.
Dept. Surgery
New Jersey Med. Sch.
185 S. Orange Ave./Room G506
Newark, NJ 07103
201-456-5045

Saba, Thomas M.
Dept. Physiology/MS 341
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5651

Sacco-Gibson, Nancy A.*
Anatomy/Medical
Loyola Univ. Chicago Med. Sch.
2160 S. First Ave.
Maywood, IL 60153
312-531-3330

Safar, Peter
Resuscitation Research Ctr.
Univ. Pittsburgh
3434 Fifth Ave.
Pittsburgh, PA 15260
412-624-6735

Sakane, Yumi
CIBA-GEIGY Corp.
556 Morris Ave./V-206
Summit, NJ 07901

Samuels, Sharon B.*
Dept. Surgery
Univ. Connecticut
263 Farmington Ave.
Farmington, CT 06032
203-679-3683

Sato, Toshihide
Dept. Pathology
Univ. Maryland
10 S. Pine St./MSTF 717
Baltimore, MD 21201
301-528-3982

Sayeed, Mohammed M.
Dept. Physiology
Loyola Univ. Stritch Sch. Med.
2160 S. First Ave.
Maywood, IL 60153
312-531-3402

Schaefer, Carl F.
Dept. Anesthesiology
Univ. Oklahoma Health Sci. Ctr.
Box 26901 Research Bldg., 25R
Oklahoma City, OK 73190
405-271-2028

Schlag, Gunther
FA F Anesthesiologie
Cobenzglasse 68
Vienna, Austria/Europe A-1190

Schloerb, Paul
Dept. Surgery
Univ. Kansas Med. Ctr.
Kansas City, KS 66103

Schmahl, Frederich W.
Inst. fur Arbeits und Sozialmedizin
Wilhelmstr. 27
Tuebingen, West Germany 7400

Scholten, Donald J.*
Dept. Surgery
Michigan State Univ.
100 Michigan Ave., N.E.
Grand Rapids, MI 49503
616-774-1405

Schumer, William
Dept. Surgery
Univ. Health Sci.
Chicago Med. Sch.
North Chicago, IL 60064
312-578-3327

Schwab, Charles William
Dept. Surgery
300 Broadway
Camden, NJ 08103
609-342-3340

Sehgal, Lakshman R.
Dept. Surgery, D-6
Michael Reese Hosp. & Med. Ctr.
Lake Shore Dr. at 31st St.
Chicago, IL 60616
312-791-5580

Selkurt, Ewald E.
Dept. Physiology & Biophysics
Indiana Univ. Sch. Med.
635 Barnhill Dr.
Indianapolis, IN 46223
317-264-7772

Semrad, Susan
Med. Sci. Large Animal
Univ. Wisconsin-Madison
Sch. Vet. Med.-2015 Linden Dr. W.
Madison, WI 53706
608-263-8399

Shackford, Steven R.
UCSD Med. Ctr.
Suite H-640-A
225 Dickinson St.
San Diego, CA 92103
619-294-3864

Shah, Dhiraj M.
Dept. Surgery/ME 602
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208

Shaikh, Khaleel A.
Three Cooper Plaza
Suite 411
Camden, NJ 08103
609-342-3341

Shapiro, Marc J.
Dept. Surgery
St. Louis Univ.
1325 S. Grand Blvd.
St. Louis, MO 63104
314-577-8365

Shatney, Clayton
Dept. Surgery
Santa Clara Valley Med. Ctr.
751 S. Bascom Ave.
San Jose, CA 95128

Shaw, James H.F.
c/o Surgery Dept.
Auckland Hosp.
Auckland, New Zealand

Shennib, Hani
Dept. Surgery
Montreal Gen. Hosp.
1650 Cedar St.
Montreal, Que, Canada H3G 1A4
514-845-4052

Shepherd, Raymond E.
Dept. Physiology
LSU Med. Ctr.
1901 Perdido St.
New Orleans, LA 70112
504-582-5166

Shigematsu, Hiroshi
1st Dept. Surgery
Fac. Med. Univ. Tokyo
7-3-1 Hongo Bunkyo-ku
Tokyo, Japan 113

Shiono, Shigeru*
Dept. Traumatology
Osaka Univ. Hosp.
1-1-50 Fukushima
Fukushima-ku
Osaka 553, Japan

Shires, George Thomas, III
Dept. Surgery F-1903
New York Hosp.- Cornell Med. Ctr.
525 E. 68th St.
New York, NY 10021
212-472-4867

Short, Billie Lou
Neonatal Intensive Care
Children's Hosp. Med. Ctr.
111 Michigan Ave., N.W.
Washington, DC 20010
202-745-3315

Sibbald, William J.
Dept. Medicine
Victoria Hosp.
391 South St.
London, Ont, Canada N6A 465
519-432-5241

Siegel, John H.
Deputy Director, MIEMSS
Univ. Maryland
22 S. Greene St.
Baltimore, MD 21201
301-528-6846

Silva, Wayne E.
Dept. Surgery
Univ. Massachusetts Med. Ctr.
Worcester, MA 01605
617-856-2296

Simms, H. Hank*
Dept. Surgery, APC 144
Rhode Island Hosp.
593 Eddy St.
Providence, RI 02903

Skandalakis, Lee J.*
35 Collier Rd., N.W.
Suite 315
Atlanta, GA 30309
404-351-3750

Slater, Harvey
Mellon Pavilion
4815 Liberty Ave.
Pittsburgh, PA 15224
412-681-5788

Slotman, Gus Jay
Dept. Surgery
Rhode Island Hosp.
593 Eddy St.
Providence, RI 02902

Smith, Edward F. III
Dept. Pharmacology
Smith Kline & French Labs
P.O. Box 1539 (L-510)
King of Prussia, PA
19406-0939
215-270-6061

Smith, J. Stanley
Dept. Surgery
MS Hershey Med. Ctr.
P.O. Box 850
Hershey, PA 17033
717-531-8955

Spath, James A.
Dept. Physiology
Thomas Jefferson Univ.
1020 Locust St.
Philadelphia, PA 19107
215-829-8819

Spence, Richard K.
Med. Arts Bldg./8th Floor
300 Broadway
Camden, NJ 08103
609-342-2000

Spillert, Charles R.
Surgery/Med. Sci. Bldg. G505
UMDNJ–New Jersey Med. Sch.
185 S. Orange Ave.
Newark, NJ 07103
201-456-4530

Spitzer, John J.
Dept. Physiology
Louisiana State Med. Ctr.
1901 Perdido St.
New Orleans, LA 70112
504-568-6172

Spitzer, Judy A.
Dept. Physiology & Med.
Louisiana State Med. Ctr.
1901 Perdido St.
New Orleans, LA 70112
504-568-6175

Sprung, Charles L.
Section of Critical Care Med.
VA Med. Ctr. (111)
1201 N.W. 16th St.
Miami, FL 33125
305-324-3153

Stein, Marshall D.
Shriners Burns Inst.
610 Texas Ave.
Galveston, TX 77550
713-756-3674

Steingrub, Jay S.
15 McIntosh Dr.
Wilbraham, MA 01095

Stephan, Rabie N.
Dept. Surgery
Michigan State Univ.
B424 Clinical Ctr.
E. Lansing, MI 48824
517-355-3310

Stith, Rex D.
Dept. Physiology
Univ. Oklahoma Hlth. Sci. Ctr.
PO Box 26901
Oklahoma City, OK 73190
405-271-2226

Stothert, Joseph C., Jr.
Dept. Surgery
Univ. Texas Med. Branch
301 Univ. Blvd.
Galveston, TX 77550
409-765-7097

Strauch, Gerald O.
Dept. Surgery
New Britian Gen. Hosp.
New Britian, CT 06050
203-224-5513

Straughn, Fred K.*
7777 Forest Lane
Bldg. A, Floor 12
Dallas, TX 75230
214-788-6812

Stremple, John
Dept. Surgery
V.A. Hosp.
University Dr. C
Pittsburgh, PA 15240
412-683-3000

Su, Jing-Yi
Dept. Pathophysiology
Beijing Med. Univ.
Xue Yuan Rd.
Beijing, China

Sugerman, Harvey J.
Dept. Surgery
Med. Col. Virginia
Box 519
Richmond, VA 23229
804-786-0032

Sumpio, Bauer E.
Dept. Surgery
Yale Univ. Sch. Med.
333 Cedar St.
New Haven, CT 06510

Talucci, Raymond C.
Dept. Surgery
Three Cooper Plaza
Suite 411
Camden, NJ 08103
609-342-3011

Tang, Chaoshu
Dept. Pathophysiology
Beijing Med. Univ.
Xue Yuan Rd.
Beijing, China

Taylor, Fletcher B.
Thrombosis/Hematol. Res. Progr.
Oklahoma Med. Research Fndn.
825 N.E. 13th St.
Oklahoma City, OK 73104

Taylor, Glen A.
Dept. Surgery
Sunnybrook Med. Ctr.
2075 Bayview Ave.
Toronto, Ont, Canada M4N 3M5
416-487-5315

Teba, Luis
Anesthesiology-Crit. Care
West Virginia Univ.
Morgantown, WV 26506
304-293-5411

Teller, John D.
Cardiovascular Disease
The Upjohn Company
RD #4, Box 445/Turf Dr.
Freehold, NJ 07728

Tempel, George E.
Dept. Physiology
Med. Univ. South Carolina
171 Ashley Ave.
Charleston SC 29425
803-792-2977

Templeton, Charles B.
Pathophysiology Div.
USAMRIID
Ft. Detrick, MD 21701
301-663-7181

Thomson, Stewart J.S.
34 Deane Crescent
Northmead Ext 7
Benoni 1500, South Africa

Till, Gerd O.
Dept. Pathology
Univ. Michigan Med. Sch.
1315 Catherine Rd.
Ann Arbor, MI 48109
313-747-2921

Todd, Thomas R.J.
Toronto Gen. Hosp.
101 College St./10 EN
Toronto, Ont, Canada M5G 1L7
416-595-3427

Toledo-Pereyra, Luis H.
Dept. Surgery
Mount Carmel Mercy Hosp.
6071 W. Outer Dr.
Detroit, MI 48235

Torma, Michael J.
Med. Ctr. Scott/SG
Scott AFB, IL 62225
618-256-7456

Torpey, David J.
Dept. Anesthesiology
Allegheny Gen. Hosp.
320 E. North Ave.
Pittsburgh, PA 15212
412-237-3156

Toth, Phillip D.
Midwest Res. Inst., Inc.
3266 N. Meridian St.
Suite 203
Indianapolis, IN 46208
317-924-5884

Traber, Daniel L.
Anesthesia Research
Shriners Burns Inst.
610 Texas Ave.
Galveston, TX 77550
409-761-1642

Traber, Lillian D.*
Dept. Anesthesiology
Univ. Texas Med. Branch
610 Texas Ave.
Galveston, TX 77550
409-761-1642

Traverso, William L.
Mason Clinic
1100 Ninth Ave.
P.O. Box 900
Seattle, WA 98111
206-223-8855

Treat, Richard C.
Surgery/Trauma Burn Serv.
Med. Col. Georgia
1120 15th St.
Augusta, GA 30912
404-721-3153

Trentz Otmar L.
Dept. Surgery–Trauma
Univ. Saarland
Chirurgische Univ. Klinik
Homburg S, West Germany 665

Troop, Bryan
621 S. New Ballas, 1017
St. Louis, MO 63141

Trooskin, Stanley Z.
Dept. Surgery
UMDNJ-Rutgers Med. Sch.
CN 19
New Brunswick, NJ 08903
201-937-7920

Trump, Benjamin F.
Dept. Pathology
Univ. Maryland
10 S. Pine St.
Baltimore, MD 21201

Trunkey, Donald
Dept. Surgery
Oregon Health Sci. Univ.
3181 S.W. Sam Jackson Park Rd.
Portland, OR 97201
503-225-7758

Turinsky, Jiri
Dept. Physiology
Albany Med. Col.
47 New Scotland Ave.
Albany, NY 12208
518-445-5659

Turner, Susan J.*
Med. Sci.
Upjohn Co. of Canada
397 Manning Ave.
Toronto, Canada M6G 2V6
416-929-3249

Ulevitch, Richard J.
Dept. Immunopathology
Scripps Clinic & Research Fndn.
10666 N. Torrey Pines Rd.
La Jolla, CA 92037

Unger, Lauren S.*
Physiology and Biophysics
Univ. Louisville
A1110 Health Sci. Ctr.
Louisville, KY 40292
502-588-7571

Urbaschek, Bernhard
Inst. Hygiene & Med./Micro.
Univ. Heidelberg Sch. Med.
6800 Mannheim 1
D6–5, West Germany

Urbaschek, Renate
Dept. Immunol. and Serol.
Inst. Med. Microbiol. and Hyg.
D6,5
Mannheim, FRG 6800

Van Der Meer, Cornelis**
Dept. Pharmacology
Univ. Amsterdam
Polderweg 104
Amsterdam, Netherlands 1093 KP

Van Kesteren, R.G.
Univ. Hosp.
Dept. Reanimation and
Clinical Toxicology
Utrecht, Netherlands 3500 CQ

Vargish, Thomas
Dept. Surgery
Univ. Chicago
5841 S. Maryland Ave.
Chicago, IL 60637
312-702-5826

Vary, Thomas C.
Dept. Physiology
Milton S. Hershey Sch. Med.
Pennsylvania State Univ.
Hershey, PA 17033

Velasco, Irineu
Res. Div.
The Heart Inst.
Caixa Postal 11450
Sao Paulo, SP
Brazil 05499

Vincent, Jean-Louis
Dept. Intensive Care
Erasme Univ. Hosp.
Route De Lennick 808
Brussels, Belgium 1070

Viray, Rico E.*
Dupont Critical Care
1600 Waukegan Rd.
Waukegan, IL 60085

Wade, Charles E.*
Military Trauma
LAIR
SGRD-UL-MT
San Francisco, CA 94129
415-561-5816

Watkins, W. David
Dept. Anesthesiology
P.O. Box 3094
Duke Univ. Med. Ctr.
Durham, NC 27710

Weil, Max
Univ. Health Sci
Chicago Med. Sch.
North Chicago, IL 60064

Weireter, Leonard*
Dept. Surgery
Eastern Virginia Med. Sch.
825 Fairfax Ave.
Norfolk, VA 23507
804-446-8950

Welch, Gary W.
Dept. Anesthesia
Univ. Massachusetts
55 Lake Ave. N.
Worcester, MA 01655

Whidden, Stanley John
Baromed. Research Inst.
JESMC
2917 Pyrtania
New Orleans, LA 70115
504-361-3996

White, Gary L.
Animal Resources
Univ. Okla Health Sci. Ctr.
P.O. Box 26901
Oklahoma City, OK 73104

Williams, Lester F.
Dept. Surg. Service
VA Med. Ctr.
1310 24th Ave. South
Nashville, TN 37212
615-327-5356

Wilmoth, Frank R.
Dept. Physiology
Univ. South Florida
12901 N. 30th St.
Tampa, FL 33612
813-974-2527

Wilson, Michael F.
Dept. Med. & Radiobiology
V.A. Med. Ctr. (151)
921 N.E. 13th St.
Oklahoma City, OK 73104
405-272-9876

Wilson, Robert F.
Dept. Surgery
Wayne State Univ.
6C-UHC
4201 St. Antoine
Detroit, MI 48201

Winn, Robert K.
Dept. Surgery ZA-16
325 9th Ave.
Seattle, WA 98104

Wise, W. Curtis
Dept. Physiology
Med. Univ. South Carolina
171 Ashley Ave.
Charleston, SC 29403

Wisner, David H.
Dept. Surgery
UCD Med. Ctr.
4301 X St., Rm. 2310
Sacramento, CA 95817
916-453-8298

Witek-Janusek, Linda
Dept. Physiology
Loyola Univ. Med. Ctr.
2160 First Ave.
Maywood, IL 60153
312-531-3330

Wolfe, Robert R.
Metabolism Unit
Shriners Burns Inst.
610 Texas Ave.
Galveston, TX 77550
409-761-6538

Wu, Chih-Hsiung
Dept. Surgery
Taipei Med. Col.
7F, 135 Sec 2 Gin-San S Rd.
Taipei, Taiwan (ROC) 10604

Yamamoto, Yasuhiro
Nippon Med. Sch.
1-1-5 Sendagi
Bunkyo-ku
Tokyo, Japan

Yelich, Michael R.
Dept. Physiology
Loyola Univ. Med. Ctr.
2160 S. First Ave.
Maywood, IL 60153
312-531-3330

Yeston, Neil S.
Hartford Hosp.
80 Seymour St.
Hartford, CT 06115

Young, Jamie S.*
Dept. Physiology
Univ. Virginia Sch. Med.
Box 449, Jordan Hall
Charlottesville, VA 22908

Young, Wise
Dept. Neurosurgery
N.Y.U. Med. Ctr.
550 First Ave.
New York, NY 10016
212-340-6316

Yu, Thomas L.*
Boston Univ. Hosp.
Dept. Laboratory Med.
88 E. Newton St.
Boston, MA 02118

Zaloga, Gary P.
Anesthesia/Crit. Care Med.
Bowman Gray Sch. Med.
300 S. Hawthorne Rd.
Winston-Salem, NC 27103
919-748-2927

Zapol, Warren M.
Dept. Anesthesia
Massachusetts Gen. Hosp.
Fruit St.
Boston, MA 02114
617-726-3030

Zeller, W. Patrick
Pediatr. Endocr. Metabol. & Nutr.
Loyola Univ. Med. Ctr.
2160 S. First Ave.
Maywood, IL 60153
312-531-4034

LISTING BY STATE

ALABAMA
Nelson, Karl M.
Rodning, Charles B.

ARIZONA
Bajo, Thomas
Carmona, Richard
McCuskey, Robert S.

ARKANSAS
Cone, John B.

CALIFORNIA
Abraham, Edward
Arfors, Karl E.
Blaisdell, F. William
Emerson, Thomas E.
Gunther, Robert A.
Holcroft, James W.
Ishida, Kimiko
Kramer, George C.
Lewis, Frank R.
Marshall, Lawrence F.
Mihm, Frederick
O'Benar, John D.
Ransom, Kenneth J.
Shackford, Steven R.
Shatney, Clayton
Ulevitch, Richard J.

COLORADO
Casey, Kenneth F.
Fettman, Martin J.
Moore, Ernest E.
Phillips, Robert W.

CONNECTICUT
Colucci, Robert D.
Ligas, James R.
McIntosh, Tracy K.
Morgan, Anthony S.
Strauch, Gerald O.
Sumpio, Bauer E.
Yeston, Neil S.

DELAWARE
Baker, Robert J.
Fagraeus, Lennart
Hubbard, Joel D.

DISTRICT OF COLUMBIA
Geelhoed, Glenn W.
Harmon, John W.
Holaday, John W.
Short, Billie Lou

FLORIDA
Baker, Carleton H.
Balis, John U.
Cavanagh, Denis
Flynn, Timothy C.
Neiberger, Richard E.
Rao, Papineni
Reynolds, David G.
Sprung, Charles L.
Wilmoth, Frank R.

GEORGIA
Hall, Edward L.
Moore, James N.
Procter, Charles D.
Reese, Andy C.
Reichard, Sherwood M.
Rickert, William B.
Skandalakis, Lee J.
Treat, Richard C.

HAWAII
McNamara, J. Judson

ILLINOIS
Alverdy, John C.
Barrett, John A.
Carroll, Gilbert C.
Ferguson, James L.
Filkins, James P.
Goto, Masakatsu
Gould, Steven A.
Griffin, Andrew J.
Hall, John R.
Jones, Stephen
Klein, Diane M.
Kober, Philip M.
Moss, Gerald S.
Rackow, Eric C.
Raymond, Richard M.

Rosen, Arthur L.
Sacco-Gibson, Nancy A.
Sayeed, Mohammed M.
Schumer, William
Sehgal, Lakshman R.
Torma, Michael J.
Vargish, Thomas
Viray, Rico E.
Weil, Max
Witek-Janusek, Linda
Yelich, Michael R.

IOWA

Ephgrave, Kimberly S.
Gurll, Nelson J.

INDIANA

Babbs, Charles F.
Badylak, Stephen F.
Bottoms, Gerald D.
Cronen, Paul
Fessler, John F.
Herron, David K.
Johnson, Martha A.
Majerus, Thomas C.
Selkurt, Ewald E.
Toth, Phillip D.

KANSAS

Schloerb, Paul

KENTUCKY

Asher, Eleanor F.
Cryer, Henry M.
Garrison, Richard N.
Groff, Diller B.
Harris, Patrick D.
Luebbe, Andreas S.
Mullins, Richard J.
Passmore, John C.
Rink, Richard D.
Unger, Lauren S.

LOUISIANA

Bagby, Gregory J.
Barker, Louis A.
Bowen, John C.
Kerstein, Morris D.
Lang, Charles
McDonough, Kathleen H.
McSwain, Norman E.
Miller, Harvey I.
Shepherd, Raymond E.
Spitzer, John J.
Spitzer, Judy A.
Whidden, Stanley John

MARYLAND

Allo, Maria D.
Breslow, Michael J.
Bulkley, Gregory B.
Clemens, Mark G.
Cowley, R. Adams
Dunham, C. Michael
Feuerstein, Giora Z.
Gann, Donald S.
Haddy Francis J.
Lamonica, Concetta R.
Malcolm, Diana S.
Marzella, Louis
Militello, Philip
Romanosky, Albert J.
Roth, Bryan L.
Sato, Toshihide
Siegel, John H.
Templeton, Charles B.
Trump, Benjamin F.

MASSACHUSETTS

Botan, Edward A.
Burke, John F.
Chernow, Bart
Demling, Robert H.
Durkot, Michael John
Fiddian-Green, Richard
Fink, Mitchell P.
Grindlinger, Gene A.
Martyn, Jeevendra
Silva, Wayne E.
Steingrub, Jay S.
Welch, Gary W.
Yu, Thomas L.
Zapol, Warren M.

MICHIGAN

Chaudry, Irshad H.
Coran, Arnold G.
Corum, T.R.
Dahn, Michael S.
Geiser, Ronald W.
Greenfield, Lazar J.
Guice, Karen S.

Harkema, James M.
Haupt, Marilyn T.
Hauptman, Joe
Hinshaw, Daniel B.
Jain, Krishna M.
Joyce, Harry H.
Ledgerwood, Anna M.
Lucas, Charles E.
Ochoa, Ricardo
Oldham, Keith
Plemmons, Bob C.
Scholten, Donald J.
Stephan, Rabie N.
Till, Gerd O.
Toledo-Pereyra, Luis H.
Wilson, Robert F.

MINNESOTA

Antonenko, David R.
Cerra, Frank B.
Paxson, Charles L.

MISSISSIPPI

Markov, Angel K.

MISSOURI

Adams, H. Richard
Baue, Arthur E.
Bessey, Palmer Q.
Brown, Danley F.
Cornell, Robert P.
Fish, Richard E.
Helling, Thomas S.
Liu, Maw-Shung
Parker, Janet L.
Troop, Bryan

NEW JERSEY

Blackwood, James M.
Flancbaum, Louis J.
Glenn, Thomas M.
Hock, Carl E.
Kelly, Kathleen M.
Lee, Bing C.
Machiedo, George W.
Nance, Francis C.
Oei, Howard
Rush, Benjamin F.
Sakane, Yumi
Schwab, Charles William
Shaikh, Khaleel A.
Spence, Richard K.
Spillert, Charles R.
Talucci, Raymond C.
Teller, John D.
Trooskin, Stanley Z.

NEW MEXICO

Fry, Donald E.

NEW YORK

Altura, Burton M.
Benjamin, Ernest
Blumenstock, Frank A.
Cho, Eshin
Dutton, Robert
Fantini, Gary A.
Flint, Lewis M.
Fortune, John B.
Gentili, David R.
Goldfarb, Roy D.
Goodwin, Cleon W.
Gumbs, Milton A.
Halevy, Simon
Halpern, Neil A.
Iberti, Thomas J.
Kaplan, John E.
Kreis, David J.
Leibowitz, David A.
Levenson, Stanley M.
Loegering, Daniel J.
McConn, Rita
Moss, Gerald
Nagler, Arnold
Pearce, Frederick J.
Rogers, Charles E.
Saba, Thomas M.
Shah, Dhiraj M.
Shires, III, George Thomas
Turinsky, Jiri
Young, Wise

NORTH CAROLINA

Carroll, Robert G.
Lundberg, Dag
Proctor, Herbert J.
Watkins, W. David
Zaloga, Gary P.

OHIO
Alexander, J. Wesley
Furste, Wesley L.
Nelson, Robert M.
Panacek, Edward A.
Rhodes, Robert S.

OKLAHOMA
Archer, Linda T.
Beller, Beverly K.
Brackett, Daniel J.
Hamburger, Steven A.
Hill, Molly R.
Hinshaw, Lerner B.
Massion, Walter H.
McCallum, R.E.
Schaefer, Carl F.
Taylor, Fletcher B.
White, Gary L.
Wilson, Michael F.

OREGON
Connell, Reid S.
Harrison, Marvin W.
Mela-Riker, Leena M.
Trunkey, Donald

PENNSYLVANIA
Alteveer, Robert J.
Angelakos, Evangelos T.
Brotman, Sheldon
Burns, J. Robert
Flynn, John T.
Geer, Ralph T.
Goldfarb, I. William
Grenvik, Ake
Hitner, Henry W.
Hoffman, James P.
Johnson, III, Gerald
Kilpatrick-Smith, Laurie
Kohler, John P.
Lanza-Jacoby, Susan
Lefer, Allan M.
Marshall, Bryan E.
Marshall, Carol
Martin, Louis F.
Peitzman, Andrew P.
Rowe, Marc I.
Safar, Peter
Slater, Harvey
Smith, III, Edward F.
Smith, J. Stanley
Spath, James A.
Stremple, John
Torpey, David J.
Vary, Thomas C.

RHODE ISLAND
Albina, Jorge
Burchard, Kenneth W.
Caldwell, Michael D.
Greenburg, A. Gerson
Maksad, Ali K.
Slotman, Gus Jay

SOUTH CAROLINA
Abel, Francis L.
Bond, Robert F.
Cook, James A.
Halushka, Perry V.
Reines, H. David
Tempel, George E.
Wise, W. Curtis

TENNESSEE
Enderson, Blaine L.
Fabian, Timothy C.
Fletcher, John Raymond
Karlstad, Michael D.
Kudsk, Kenneth A.
Lobe, Thom E.
McCoy, Sue
Patterson, C. Richard

TEXAS
Canizaro, Peter C.
Carvajal, Hugo F.
Dawidson, Ingemar J.A.
Dehring, Deborah J.
Feola, Mario
Fischer, Ronald P.
Gill, William
Herndon, David N.
Horton, Jureta
Houtchens, Bruce A.
Illner, Hana P.
Janssen, Herbert F.
Kutsky, Phyllis B.
Lutherer, Lorenz O.
Pruitt, Jr., Basil A.
Reed, R. Lawrence
Stein, Marshall D.
Stothert, Jr., Joseph C.
Traber, Daniel L.
Traber, Lillian D.

Wolfe, Robert R.

VIRGINIA
Gervin, Alfred S.
Hess, Michael L.
Longnecker, David E.
Sugerman, Harvey J.
Young, Jamie S.

WASHINGTON
Carrico, C. James
Harlan, John M.
Herman, Clifford M.
Langdale, Lorrie A.
Maier, Ronald V.
Pohlman, Timothy H.
Rice, Charles L.
Traverso, William L.
Winn, Robert K.

WEST VIRGINIA
Beamer, Kathryn C.
James, Jr., Paul M.
Teba, Luis

WISCONSIN
Semrad, Susan

LISTING BY COUNTRY

AUSTRIA
Schlag, Gunther

BELGIUM
Vincent, Jean-Louis

BRAZIL
Velasco, Irineu
Rocha-e-Silva, Mauricio

CANADA
Chiu, Ray Chu-Jeng
McArdle, A. Hope
Mulder, David S.
Naylor, Jonathan M.
Nelson, William R.
Pivon, Richard J.
Shennib, Hani
Sibbald, William J.
Taylor, Glen A.
Todd, Thomas R.J.
Turner, Susan J.

CHINA
Chen, Hua-Cui
Jin, Huiming
Luo, Zheng Yao
Su, Jing-Yi
Tang, Chaoshu

DENMARK
Engquist, Allan

FRANCE
Carli, Alain
Kovach, Aristztid G.B.

ISRAEL
Amir, Shimon
Bitterman, Haim
Gross, Ditza
Krausz, Michael M.

ITALY
Foca, Alfredo
Giovannini, Ivo
Matera, Giovanni
Novelli, Gian Paolo

JAPAN
Ebata, Toshiaki
Hayasaka, Hiroshi
Hirasawa, Hiroyuki
Imai, Takasuke
Kamiyama, Yasuo
Koyama, Shozo
Morita, Shigeho
Ogata, Hiromaru
Ogawa, Ryo
Ohkawa, Masanori
Ohtake, Yoshio
Okabe, Eiichiro
Okada, Kazuo
Okuda, Minoru
Shigematsu, Hiroshi
Yamamoto, Yasuhiro

NETHERLANDS
Bastiaans, Johanna C.
Van der Meer, Cornelis
Van Kesteren, R.G.

NEW ZEALAND
Shaw, James H.F.

NORWAY
Myrvold, Helge E.

SAUDI ARABIA
Al Tuwaijri, Ali S.

SOUTH AFRICA
Gaffin, Stephen L.
Mouton, Wynand L.
Thomson, Stewart J.S.

SPAIN
Garcia-Barreno, Pedro

SWEDEN
Biber, Bjorn
Haglind, Eva
Haglund, Ulf
Haljamae, Hengo
Lewis, David H.
Risberg, Bo I.

SWITZERLAND
Doran, Jan Eva
Lundsgaard-Hansen, P.

TAIWAN (ROC)
Wu, Chih-Hsiung

UNITED KINGDOM
Little, Roderick A.
Parratt, James R.

WEST GERMANY
Ball, Howard A.
Horpacsy, Geza
Keppler, Dietrich
Oestern, Hans-Jorg
Schmahl, Frederich W.
Trentz, Otmar L.
Urbaschek, Bernhard

Author Index to Volume 27

Subject Index to Volume 27

CIRCULATORY SHOCK

Volume 27, 1989

James P. Filkins
Editor

Alan R. Liss, Inc.

41 East 11th Street
New York, NY 10003

Contents

Volume 27, Number 1 January 1989

Volume 27, Number 4 **April 1989**

THE TWELFTH ANNUAL CONFERENCE ON SHOCK
June 9–12, 1989
Marco Island, Florida

CIRCULATORY SHOCK

Revised December 1988

INSTRUCTIONS FOR CONTRIBUTORS

CIRCULATORY SHOCK will accept original contributions concerned with significant new developments in basic or clinical shock research. The research may deal with biochemical, physiological, pharmacological, morphological, pathological, medical, or surgical aspects of circulatory shock and related states. Short papers (normally 2–3 printed pages) on a unique finding, new phenomenon, or novel technique will also be considered. Concise review articles and position papers are invited. The Editor welcomes suggestions about prospective authors and topics.

Manuscripts and all editorial correspondence should be sent to Dr. James P. Filkins, Department of Physiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153.

MANUSCRIPTS. Submit the original and three copies of the manuscript (including tables and illustrations) typed on one side of good quality 8½ × 11 inch paper with at least one inch margins. Double space everything. Start a new page for each major division of the manuscript. Number all pages in sequence beginning with the title page. Arrange the copy in the following order:

TITLE PAGE. This should contain the complete title of the manuscript, names and affiliations of all authors, institution at which the work was performed, name and address for correspondence, and a running head of not more than 45 characters.

ABSTRACT. This should consist of 100–150 words summarizing the major findings and conclusions in the paper.

KEY WORDS. Submit five to ten key words appropriate for the article which will be used for indexing purposes. Do not repeat words or terms used in the title.

TEXT. The text should follow the format: introduction, materials and methods, results, discussion, and conclusions. Use subheadings and paragraph titles whenever possible. For abbreviations, follow the guidelines in Council of Biology Editors Style Manual, 5th edition (available from the Council of Biology Editors, Inc., 9650 Rockville Pike, Bethesda, MD 20814). Use generic names for all drugs and pharmaceutical preparations. Trade names, along with manufacturer and location may be mentioned in the Methods section. Place acknowledgments as the last element of the text, before references.

REFERENCES. In the text, references should be cited consecutively by numbers in brackets. In the final list, they should be in numerical order, include the complete title of the article cited, and names of all authors. Journal abbreviations should follow *Index Medicus* style. In the following examples notice the punctuation, do not use all capitals, do not underline.

Journal articles:

1. Stahl GL, Lefer AM: Heterogeneity of vascular smooth muscle responsiveness to lipid vasoactive mediators. Blood Vessels 24:24–30, 1987.

Books:

2. Kaneko JJ: Clinical Biochemistry of Domestic Animals. New York: Academic Press, 1980, p 110.

Articles in books:

3. Walker RI, Casey LC: Endotoxin interactions with platelets. In Berry LJ (ed): "Cell Biology of Endotoxin." Amsterdam: Elsevier, 1985, p 225.

TABLES. Tables must be numbered in order of appearance with Roman numerals. Each must have a title and be keyed into the text.

LEGENDS. A legend must accompany each illustration and must define all abbreviations used therein.

ILLUSTRATIONS. Glossy black-and-white photographs 5″ × 7″ or 8″ × 10″ in size are preferred. Color will be printed only at the author's expense. The charge for one page of color is $950. Second and subsequent pages, up to four, will cost $500 each. Do not submit original recordings, graphs, radiographic plates, or art work. They will be requested at a later date if needed for publication. All lettering must meet professional standards (and must be legible after reduction in size); typewritten or hand lettering is unacceptable. All illustrations must be numbered in order of appearance with arabic numerals. Identify each illustration on the back by affixing a gummed label on which is listed: the number of the illustration, name of the illustration, name of first author, title of manuscript, and an arrow indicating the top.

ALL MANUSCRIPTS submitted to *Circulatory Shock* must be submitted solely to this journal, may not have been published in any part or form in another publication of any type, professional or lay, and become the property of the publisher. Upon acceptance of a manuscript for publication, the author will be requested to sign an agreement transferring copyright to the publisher, who reserves copyright. No published material may be reproduced or published elsewhere without the written permission of the publisher and the author. The journal will not be responsible for the loss of manuscripts at any time. All statements in, or omissions from, published manuscripts are the responsibility of the authors, who will assist the editors by reviewing proofs before publication. Manuscripts involving human subjects must state approval by institutional human experimentation review committees. Manuscripts involving laboratory animals must state adherence to the NIH guidelines for the use of experimental animals. Reprint order forms will be sent with the proofs.

CIRCULATORY SHOCK
OFFICIAL JOURNAL OF THE SHOCK SOCIETY AND OF THE EUROPEAN SHOCK SOCIETY

Volume 27, Number 4 April 1989

THE TWELFTH ANNUAL CONFERENCE ON SHOCK
June 9–12, 1989
Marco Island, Florida